Dossier for *Requip® XL™* (ropinirole extended-release tablets) in Parkinson's Disease (PD)

Dossier for *Requip® XL™* (ropinirole extended-release tablets) in Parkinson's Disease (PD)

This information is provided in response to your request for information about Requip® XL™ (ropinirole extended-release tablets).

Some information contained in this response may not be included in the approved Prescribing Information. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.

In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.

This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

TABLE OF CONTENTS

1. Change Summary

1. **Sections 3.14 & 4.3:** Added reference by 2008 Stocchi F, et al. (EASE PD Monotherapy Study).
2. **Section 4.3:** Added table for adverse events by dose for EASE PD Monotherapy Study.
3. **Section 4.1:** Added 3 references for the PREPARED Study- 2008 Schapira AHV, et al (2 posters) and 2008 Stocchi F, et al. (1 poster).
4. **Sections 3.3, 3.3 & 3.4:** Added 12 mg tablet dosage form, package size, NDC number and WAC price.

2. EXECUTIVE SUMMARY

Parkinson's Disease Management - Introducing Requip® XL™ (ropinirole) Extended-Release Tablets

Parkinson's disease (PD), like other chronic diseases, often requires long-term treatment. Patients with PD often take multiple medications and face significant daily pill burden in managing their disease often making them susceptible to suboptimal adherence and, therefore, suboptimal management with increased expenses.

Complex medication regimens, including taking multiple medications or frequent dosing, have been linked to poor medication adherence in patients with PD as well as in other chronic conditions.[1,2,3,4,5,6]

Several studies that evaluated medication adherence in patients taking PD medications found patients with poor medication compliance to be younger in age, to be taking more tablets per day and have higher depression scores, poorer quality of life and worsening of PD symptoms than adherent patients.[1,2,7,8]

A survey of 250 PD patients taking IR (immediate-release) *Requip* at least three times daily found 67% to be non-adherent with only 33% categorized as adherent (i.e. no missed doses of IR *Requip* in the past week) resulting in recurrence of their PD symptoms which consequently had an effect on their normal daily activities.[9] When asked, 88% of patients indicated they would be "interested in a once-daily formulation" of *Requip* because it would be easy to remember to take.

Another analysis examined the daily pill burden of patients with PD and evaluated the potential need for *Requip XL* (a once-daily regimen).[10] Results indicated that patients with PD face a significant daily pill burden. In this study patients averaged 5 antiparkinsonian medication tablets per day with 75% of patients taking at least 3 pills per day. Approximately 44% (n=151/342) of patients in the group receiving IR *Requip* filled at least one adjuvant antiparkinsonian prescription during the 2-week identification period. This analysis highlighted the need for treatment options that can reduce this pill burden.

Please note, there are no studies examining medication adherence with patients taking *Requip XL*.

The Role of Dopamine Agonists in PD

2001 Treatment Guidelines published by experts on PD recommend dopamine agonists as first-line initial monotherapy for newly diagnosed PD patients, as well as adjunctive therapy to L-dopa for appropriate PD patients in an effort to decrease the risk of motor complications associated with L-dopa. [11] In addition, the 2006 American Academy of Neurology (AAN) practice parameters support the use of dopamine agonists as initial monotherapy in treating PD symptoms and lessening motor complications. [12]

Motor complications associated with the use of L-dopa are hypothesized to arise due to the pulsatile stimulation of dopamine receptors in the striatum.[13,14] One of the theoretical advantages of dopamine agonists compared to L-dopa is a longer half-life resulting in less pulsatile stimulation of dopamine receptors which may reduce the risk of dyskinesias and motor fluctuations.[14,15,16,17]

Therapies that provide more continuous stimulation of dopamine receptors have been found to reduce motor complications in monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and in patients with PD.[14,17] Continuous delivery of ropinirole (via subcutaneous infusion) in MPTP-treated marmosets has been shown to reverse motor deficits without induction of dyskinesias better than repeated oral ropinirole administration.[18] Therefore, steady delivery of ropinirole from a once-daily controlled release form of ropinirole may reduce off-time and delay or prevent the onset of L-dopa-related motor complications.

Requip XL - Description

Requip® XL™ (ropinirole extended-release tablets) is the only once-daily oral dopamine agonist FDA-approved for the treatment of the signs and symptoms of idiopathic PD.[19] *Requip XL* tablets are composed of an innovative tri-layer formulation that allows a steady rate of absorption with fewer fluctuations in ropinirole concentration over 24 hours compared to IR *Requip* given three times daily.[20] *Requip XL* offers a simple titration regimen; it also offers a convenient, once-daily dosing schedule compared to other oral dopamine agonists, which are dosed multiple times a day.

Requip XL - Efficacy for PD

***Requip XL* vs. IR *Requip* as adjunctive therapy in PD:**

A 6-month, randomized, double-blind study in patients with advanced PD (N= 350) not optimally controlled on L-dopa found the following results in patients treated with adjunctive *Requip XL* compared to IR *Requip*:[21,22,23,24,25,26]

- Significantly more patients receiving *Requip XL* (64%, 110/172) **maintained a ≥ 20% reduction in "off" time** compared to those receiving IR *Requip* (51%, 85/168).
- Significantly more patients receiving *Requip XL* had improved Clinical Global Impression-Improvement (CGI-I) scale scores (55%, 95/173) vs. those receiving IR *Requip* (43%, 73/168).
- The mean adjusted change from baseline in Unified Parkinson's Disease Rating Scale (UPDRS) total motor score with patients in an "on" state was significantly greater for *Requip XL* (-10.2) vs. IR *Requip* (-7.9).

***Requip XL* as adjunctive therapy in PD:**

A 6-month, placebo-controlled trial in patients with advanced PD receiving concomitant L-dopa, found that patients treated with *Requip XL* (n=201) compared to placebo (n=190) had the following:[27]

- Significantly **reduced daily "off" time** [within 2 weeks (-1.1 hrs/day) and continued through 6 months (-2.1 hrs/day) vs. -0.3 hrs/day placebo (PBO)].
- **Improved CGI-I scores** (42% of patients receiving *Requip XL* vs. 14% of PBO patients).
- **Reduced L-dopa dose** [34% (278 mg/day) *Requip XL* vs. 21% (164 mg/day) PBO]. The mean daily dose of *Requip XL* at study endpoint was 18.8 mg/day.
- **Increased "on" time without troublesome dyskinesias** (1.6 hours *Requip XL* vs. PBO).
- **Improved activities of daily living (ADLs)** (25% improvement in patients receiving *Requip XL* vs 6% improvement in PBO patients).
- **Improved UPDRS motor performance scores** (22% improvement in patients receiving *Requip XL* vs 6% improvement in PBO patients), including improvement in UPDRS items of tremor, rigidity and bradykinesia (cardinal symptoms of PD).
- *Requip XL* also improved other secondary endpoints including: Beck Depression Inventory-II (BDI-II) total score; Parkinson's Disease Quality of life questionnaire (PDQ-39) subscores (mobility, ADLs, emotional well-being, stigma, communication), and Parkinson's Disease Sleep Scale (PDSS) total score. The PDQ-39 subscores of social support, cognition, and bodily discomfort did not reach statistical significance nor did the Epworth Sleepiness Scale (ESS) total scores.

***Requip XL* as initial monotherapy in PD:**

A 36-week, double-blind, three-period, crossover study with *Requip XL* vs. IR *Requip* in patients (N=161) with early PD found that the effectiveness of ***Requip XL* once daily was equivalent to IR *Requip* three times daily** based on the following:[28]

- **Similar daily doses of each formulation produced similar efficacy**, as indicated by maintained UPDRS scores when patients switched formulations.
- **Both formulations were effective in relieving motor symptoms in patients with early PD, as well as improving ADL scores, CGI-I scores, BDI-II scores, ESS scores and Parkinson's Disease Sleep Scale (PDSS) scores.**

***Requip XL* and onset of dyskinesia in PD:**

A multicenter, randomized, double-blind, L-dopa-controlled, flexible-dose study in patients with advanced PD evaluated the time to onset of dyskinesia during adjunctive therapy with *Requip XL* compared to adjunctive L-dopa.[29] Patients had been taking ≤ 600 mg L-dopa for up to 3 years without optimal symptom control. The study was terminated early nearly 2 years after initiation when a review of the study indicated that enrollment was lower than the projected sample size needed. However, a post-hoc analysis showed a **significant delay in the onset of dyskinesia** in the group receiving *Requip XL* vs. the L-dopa group.

Requip XL - Safety Profile

- The most common adverse reactions (incidence ≥5% and greater than placebo) in advanced PD patients with concomitant L-dopa were dyskinesia, nausea, dizziness, hallucination, somnolence, abdominal pain/discomfort, and orthostatic hypotension.(27)
- The most common adverse reactions (incidence ≥5%) in early PD without L-dopa were nausea, somnolence, abdominal pain/discomfort, dizziness, headache, and constipation.(28)
- See the enclosed Prescribing Information for more details on labeled Warnings, Precautions and Patient Counseling Information.(19)

Requip XL - Dosing

Dosing *Requip XL*:

- The starting dose for *Requip XL* is 2 mg once daily for 1 to 2 weeks, followed by increases of 2 mg/day at 1-week or longer intervals as appropriate. See Table 1.(19)

Table 1. Dosing Regimen for *Requip XL*

Step	Individual Dose (QD)	Total Daily Dose	Duration
1	2 mg	2 mg/day	1 to 2 weeks
2	4 mg	4 mg/day	1 week or longer
3	6 mg	6 mg/day	1 week or longer
4	8 mg	8 mg/day	1 week or longer
• Increase dosage by 2 mg/day at 1- to 2-week intervals (or longer if appropriate), depending on therapeutic response and tolerability up to a maximum dose of 24 mg/day. • Patients should be assessed for therapeutic response and tolerability at a minimum interval of 1 week or longer after each dose increment.			

Switching from IR *Requip* to *Requip XL*:

- Appropriate patients may be switched directly from IR *Requip* to *Requip XL* with an initial switching dose of *Requip XL* that most closely matches the total daily dose of IR *Requip*.(19,28,30) Following conversion to *Requip XL*, the dose may be adjusted depending on therapeutic response and tolerability.

Switching from Pramipexole to *Requip XL*:

- A conversion ratio of 1 mg pramipexole to 4 mg *Requip XL* was found to be effective in switching patients (N=60) with PD overnight from pramipexole to *Requip XL*.(31)

3. DISEASE DESCRIPTION

Overview of Parkinson's Disease

Parkinson's disease is a chronic, disabling, neurodegenerative condition attributed to a loss of dopaminergic neurons in the nigrostriatal pathway. (11) Motor symptoms of PD include resting tremor, bradykinesia, rigidity, and postural instability.(32) In addition, secondary complications associated with PD include psychiatric disorders such as depression, dementia, autonomic dysfunction, and difficulty sleeping, swallowing or speaking.

Incidence and Prevalence

Approximately 1 million people in the U.S. suffer from PD with nearly 60,000 new cases diagnosed each year. (33) The typical age of onset is 60 years and the prevalence is expected to increase as the population ages. Parkinson's disease can occur in patients before the age of 40 but it is relatively uncommon.(34,35) All racial groups can be affected, however the incidence is slightly higher in men compared to women.(36,37)

Etiology/Pathophysiology

The exact cause of PD is unknown but proposed environmental and genetic factors have been implicated. (11,38) Symptoms of PD are associated with the degeneration of dopaminergic neurons.(38,39) Onset of symptoms occurs after approximately 70 to 80% of the dopaminergic neurons connecting the substantia nigra pars compacta to the caudate nucleus have degenerated.

Diagnosis

Parkinson's Disease diagnosis is difficult in the early stages given the diagnostic criteria are not clearly defined. [11,39] A common diagnostic method based on clinical features, requires the presence of two of the following three features: tremor, rigidity and bradykinesia. [11] However, this method may lead to an incorrect diagnosis in approximately 5% to 10% of patients.[39] Parkinson's disease may be misdiagnosed as atypical parkinsonism which has the following clinical features: early onset of speech dysfunction and postural instability, greater axial rigidity than appendicular, falls early in the disease course, symmetry of motor signs at onset, dysphagia, and a poor response to levodopa. [11,39] Multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) are examples of atypical parkinsonism. [11] The following tools can be helpful to diagnose PD: clinical features, medication challenge with levodopa, genetic testing, and neuroimaging techniques.

Management

The decision to initiate therapy and use of therapeutic agents for PD should be individualized to each patient.[40] The following factors may influence the initial treatment choice: age, cognitive impairment, disease severity, threatened loss of employment, and cost of therapy. [11] Nonpharmacological treatment consists of disease education, support/counseling, exercise and nutrition. Pharmacological treatment consists of the following medication classes: anticholinergic, antiviral, monoamine oxidase B inhibitors, dopamine agonists, antiparkisonian, and catechol O-methyltransferase inhibitors. It is recommended that the choice of pharmacological treatment class be patient specific.[40] Surgical treatment is another option for patients who may not be responding to other therapies. [11] Additional details regarding PD management may be found in the following references:

- Olanow WC, Watts RL, Koller WC, An algorithm (decision tree) for the management of Parkinson's disease (2001): Treatment Guidelines. *Neurology* 2001;56(Suppl 5):S1-S88.
- Miyasaki JM, Martin W, Suchowersky O, et al. Practice parameter: Initiation of treatment for Parkinson's disease: An evidence-based review: Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2002;58:11-17.
- Pahwa R, Factor SA, Lyons KE, Ondo WG, et al. Practice Parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006;66:983-995.
- Schapira A. Treatment Options in the Modern Management of Parkinson Disease. *Arch Neurol* 2007;64(8):1083-1088.

The 2001 Treatment Guidelines for Parkinson's Disease (PD) recommend dopamine agonists as first-line initial monotherapy for newly diagnosed PD patients, as well as adjunctive therapy to L-dopa for appropriate PD patients. [11] In addition, the 2006 American Academy of Neurology (AAN) practice parameters support the use of dopamine agonists as initial monotherapy in treating PD symptoms and lessening motor complications. [12]

Motor complications secondary to L-dopa are hypothesized to arise due to the pulsatile stimulation of dopamine receptors in the striatum.[13,14] One of the theoretical advantages of dopamine agonists compared to L-dopa is a longer half-life resulting in less pulsatile stimulation of dopamine receptors which may reduce the risk of dyskinesias and motor fluctuations.[14,15,16,17]

Therapies that provide more continuous stimulation of dopamine receptors have been found to reduce motor complications in monkeys treated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and in patients with PD.[14,17] Continuous delivery of ropinirole (via subcutaneous infusion) in MPTP-treated marmosets has been shown to reverse motor deficits without induction of dyskinsias better than repeated oral ropinirole administration.[18] Therefore, steady delivery of ropinirole from a once-daily controlled release form of ropinirole may reduce off-time and delay or prevent the onset of L-dopa-related motor complications.

4. PRODUCT DESCRIPTION

4.1 Generic Name, Brand Name and Therapeutic Class

a. Generic Name: ropinirole extended-release tablets

b. Brand Name: *Requip® XL™*

c. Therapeutic Class: Nonergot-derivative Dopamine Receptor Agonist

4.2 Dosage Forms and Package Sizes

Requip XL is formulated as a three-layered tablet with a central, active-containing, slow-release layer, and 2 placebo outer layers acting as barrier layers which control the surface area available for drug release.[19] Each biconvex, capsule-shaped tablet contains 2.28 mg, 4.56 mg, 9.12 mg, or 13.68 mg ropinirole hydrochloride equivalent to ropinirole 2 mg, 4 mg, 8 mg, or 12 mg, respectively.

Requip XL is formulated with Geomatrix® technology. This technology employs a multi-layer matrix for dissolution of drug over time.[41,42,43,44,45,46] The active ingredient is located in the hydrophilic core (i.e., active-containing, slow-release layer) of the tablet with two outer, polymeric-coated layers (i.e., inert barrier layers) (See Figure 1). The two coatings around the core serve to modify the hydration and swelling rates of the active ingredient as well as lessen the surface area available for the drug to be released. This results in more constant drug release than would typically occur at a time-dependent rate.

Figure 1. Three-Layer Tablet Design for *Requip* XL[41]

* Adapted from Conte and Maggi, Biomaterials 1996

During tablet dissolution, the two outer layers remain relatively unchanged while the core swells. This allows for constant drug release over time. The multi-layer system completely dissolves at the end of the dissolution process.

Requip XL is available as biconvex, capsule-shaped, film-coated tablets in bottles of 30 tablets or 90 tablets, each in strengths of 2 mg, 4 mg, and 8 mg and 12 mg in a bottle of 30 tablets.

4.3 NDC for All Formulations

- NDC 0007-4885-13: 2 mg pink tablets in bottles of 30
- NDC 0007-4885-59: 2 mg pink tablets in bottles of 90
- NDC 0007-4887-13: 4 mg light brown tablets in bottles of 30
- NDC 0007-4887-59: 4 mg light brown tablets in bottles of 90
- NDC 0007-4888-13: 8 mg red tablets in bottles of 30
- NDC 0007-4888-59: 8 mg red tablets in bottles of 90
- NDC 0007-4882-13: 12 mg green tablets in bottles of 30

Note: A 6 mg tablet strength is under development.

4.4 WAC Cost per Unit

Table 2 summarizes the Wholesaler's Acquisition Cost (WAC) for *Requip XL*.

Table 2. WAC Pricing for *Requip XL* Tablets

NDC	Tablet Strength	Bottle Size	WAC	WAC/Tablet
0007-4885-13	2 mg	30	$65.10	$2.17
0007-4885-59	2 mg	90	$195.20	$2.17
0007-4887-13	4 mg	30	$130.20	$4.34
0007-4887-59	4 mg	90	$390.50	$4.34
0007-4888-13	8 mg	30	$195.30	$6.51
0007-4888-59	8 mg	90	$585.70	$6.51
0007-4882-13	12 mg	30	$325.42	$10.85

4.5 AHFS Drug Classification

AHFS Classification: 28.36.20.08 Nonergot-derivative Dopamine Receptor Agonists

4.6 FDA Approved Indications

REQUIP XL is indicated for the treatment of signs and symptoms of idiopathic Parkinson's disease.

4.7 Use in Special Populations

Refer to Enclosed Prescribing Information.

4.8 Pharmacology

Mechanism of Action in Parkinson's Disease

The precise mechanism of action of *Requip* XL as a treatment for Parkinson's disease is unknown, although it is believed to be due to stimulation of postsynaptic dopamine D_2-type receptors within the caudate-putamen in the brain.[19] This conclusion is supported by studies that show that ropinirole improves motor function in various animal models of Parkinson's disease.[47] In particular, ropinirole attenuates the motor deficits induced by lesioning the ascending nigrostriatal dopaminergic pathway with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in primates. The relevance of D_3-receptor binding in Parkinson's disease is unknown.

4.9 Pharmacokinetics/Pharmacodynamics

Prescribing Information

Absorption

In clinical studies with *IR Requip*, over 88% of a radiolabeled dose was recovered in urine, and the absolute bioavailability was 45% to 55%, indicating approximately 50% first pass effect.[19] Ropinirole displayed linear kinetics up to doses of 24 mg/day (8 mg immediate-release, 3 times a day). Increase in systemic exposure of ropinirole following oral administration of 2 to 12 mg of *Requip XL* was approximately dose-proportional. For *Requip XL*, steady-state concentrations of ropinirole are expected to be achieved within 4 days of dosing.

Relative bioavailability of *Requip XL* compared with immediate-release tablets was approximately 100%. In a repeat-dose study in patients with Parkinson's disease using *Requip XL* 8 mg, the dose-normalized $AUC_{(0-24)}$ and C_{min} for *Requip XL* and immediate-release ropinirole were similar. Dose-normalized C_{max} was, on average, 12% lower for *Requip XL* than for the immediate-release formulation and the median time-to-peak concentration was 6 to 10 hours. In a single-dose study, administration of *Requip XL* to healthy volunteers with food (i.e., high-fat meal) increased AUC by approximately 30% and C_{max} by approximately 44%, compared with dosing under fasted conditions. In a repeat dose study in patients with Parkinson's disease, food (i.e., high fat meal) increased AUC by approximately 20% and C_{max} by approximately 44%; T_{max} was prolonged by 3 hours (median prolongation) compared with dosing under fasted conditions.

Clinical Information

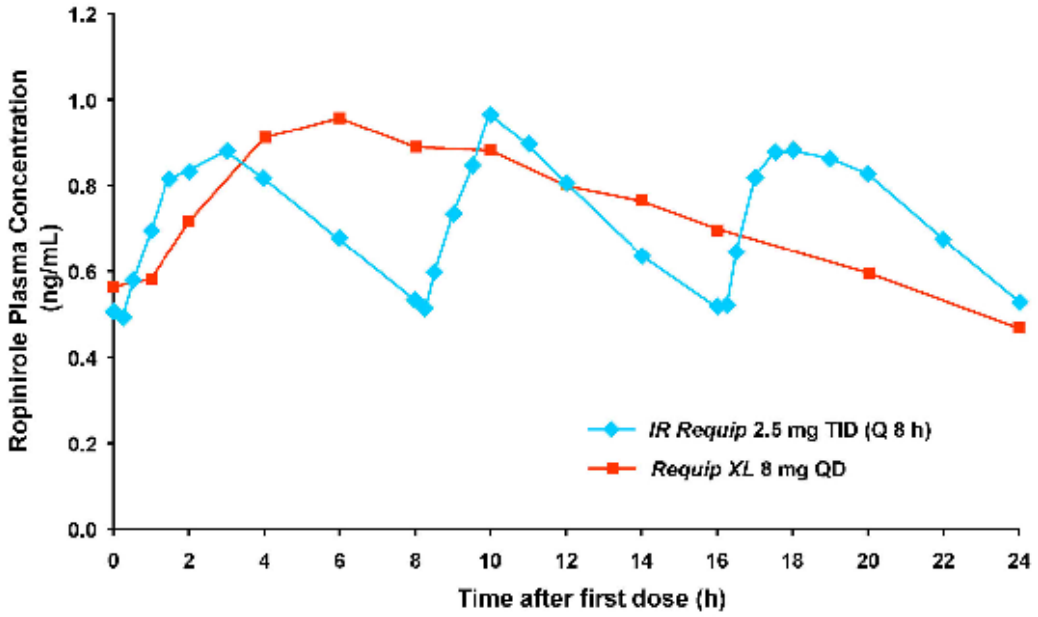
Bioavailability

A phase II, open-label, crossover study, conducted in patients with early Parkinson's disease assessed the relative bioavailability of *Requip XL* versus *IR Requip*.[20,48] Trial design and entry criteria are published

elsewhere.[20] Patients were administered either *Requip XL* 8 mg tablets once daily or *IR Requip* 2.5 mg tablets administered 3 times daily at 8-hour intervals. Following blood sampling, patients switched formulations.

The following pharmacokinetic parameters were assessed to determine relative bioavailability: $AUC_{(0-24)}$, C_{max}, and C_{min}. The degree of fluctuation and T_{max} were also assessed for each formulation of ropinirole. Nineteen of 20 patients who participated in the study provided pharmacokinetic data for assessment of relative bioavailability. After administration of *Requip XL*, the rate of absorption was slower relative to *IR Requip* and the median T_{max} occurred 6 hours post-dose (see Figure 2). For IR *Requip*, plasma concentrations of ropinirole increased rapidly with a median T_{max} of 2 hours. The $AUC_{(0-24)}$ values, normalized to dose, were similar between *Requip XL* administered once daily and *IR Requip* administered three times daily.

Figure 2. Rate of Absorption over 24 hours at steady-state: *Requip XL* vs. IR *Requip*



The C_{max} normalized to dose was approximately 12% lower for *Requip XL* versus IR *Requip*. C_{min} values were similar between the two formulations. The degree of fluctuation over 24 hours, therefore, was slightly smaller for *Requip XL*.

This pharmacokinetic study concluded that *Requip XL* allows a steady rate of absorption with fewer fluctuations in ropinirole concentration over 24 hours compared to *IR Requip* given three times daily.

4.10 Contraindications

Refer to Enclosed Prescribing Information.

4.11 Warnings/Precautions

Refer to Enclosed Prescribing Information.

4.12 Adverse Events

Refer to Enclosed Prescribing Information.

4.13 Drug/Food/Disease Interactions

Refer to Enclosed Prescribing Information.

4.14 Dosing and Administration

Switching Between IR Requip and Requip XL

Study Description

Switching between immediate-release (IR) *Requip* and *Requip XL* was examined in the Efficacy and Safety Evaluation in Parkinson's Disease (EASE-PD) Monotherapy Study.[28,49,50] The EASE-PD Monotherapy study was a 36-week, multi-center, randomized, double-blind, double-dummy, three-period, two-treatment crossover study comparing the efficacy and safety of once daily *Requip XL* to IR *Requip* three times daily in patients (N=161) with early Parkinson's disease (Hoehn & Yahr Stages I to II.5). This study was designed to demonstrate the non-inferiority of *Requip XL* to IR *Requip* as monotherapy in patients with early stage PD, as well as to provide data on switching from IR *Requip* to *Requip XL*. This study was not designed to show superiority of one formulation over the other, and therefore, not powered to demonstrate a significant difference between products.

Following a 1-week placebo run-in period, there were four phases of the study: a 12-week titration period and three 8-week flexible-dose maintenance treatment periods, for a total duration of 36 weeks. After a 1-week placebo run-in period, patients were randomized (1:1:1:1) to one of four formulation sequences as follows:

- *Requip XL* - *Requip XL* - IR *Requip*
- *Requip XL* - IR *Requip* - IR *Requip*
- IR *Requip* - IR *Requip* - *Requip XL*
- IR *Requip* - *Requip XL* - *Requip XL*

Patients entered a 12-week titration period with the first formulation in their sequence. Half of the patients started titration with IR *Requip* and half with *Requip XL*. At the end of the 12-week titration period, patients who achieved a stable Unified Parkinson's Disease Rating Scale (UPDRS) motor score entered the first 8-week maintenance period. In maintenance period 1, patients continued to receive the formulation they had received during the titration period. At the end of maintenance period 1, half the patients underwent overnight switching to the closest dose of the alternative formulation of ropinirole (i.e. IR *Requip* to *Requip XL* or *Requip XL* to IR *Requip*), the other half receiving a dummy switch. At the end of the second 8-week maintenance period, the remaining half of patients underwent overnight switching, with the other half receiving a dummy switch. Thus, by maintenance period 3, all patients had switched to the opposite formulation of ropinirole. Dose adjustments were permitted during the first 4 weeks of each maintenance period.

Dosing

Patients randomized to *Requip XL* received doses from 2 to 24 mg/day. The starting dose was 2 mg/day. Overall, eight dose levels were available (2, 4, 6, 8, 12, 16, 20 and 24 mg/day). If possible, patients received weekly fixed-dose titration (based on tolerability) over the first four weeks to a dose of *Requip XL* 8 mg/day (Dose Level 4). Further dose titration was dependent on the response/tolerance of each individual patient.

Requip XL taken once daily was compared with IR *Requip* (0.75 to 24 mg/day) taken in three divided doses. IR *Requip* had a starting dose of 0.75 mg/day and patients were then titrated to an optimal therapeutic response. Overall, a total of 13 dose levels were available (0.75, 1.5, 2.25, 3, 4.5, 6, 7.5, 9, 12, 15, 18, 21 and 24 mg/day). If possible, patients were titrated to Dose Level 4 (3 mg/day) over the first four weeks. Further dose titration was dependent on the response/tolerance of each individual patient.

At the treatment crossovers, patients were switched overnight between formulations to the nearest equivalent dose. See Table 3.

Table 3. Recommended Dose Conversion between IR *Requip* and *Requip XL*

IR *Requip to Requip XL*		*Requip XL* to IR *Requip*	
Total Daily Dose of IR *Requip* (mg)	**Total Daily Dose of *Requip XL* (mg)**	**Total Daily Dose of *Requip XL* (mg)**	**Total Daily Dose of IR *Requip* (mg)**
0.75 to 2.25	2	2	2.25
3 to 4.5	4	4	4.5
6	6	6	6
7.5 to 9	8	8	7.5
12	12	12	12
15 to 18	16	16	15
21	20	20	21
24	24	24	24

Study Results

Requip XL was found to be non-inferior to IR *Requip* in terms of efficacy in patients with early PD. Similar doses of *Requip XL* and IR *Requip* produced similar efficacy, as indicated by maintained UPDRS scores when patients switched formulations. Both *Requip XL* and IR *Requip* were effective in relieving motor symptoms in patients with early PD, as well as improving Activities of Daily Living (ADL) scores and Clinical Global Impression-Improvement (CGI-I) scores.

Adverse events were similar between formulations, although patients were titrated faster and to higher doses sooner with *Requip XL* than IR *Requip*. There was no indication that the incidence of adverse events increased during the time periods immediately following formulation switch. No patients required a reduction in dose due to experiencing an adverse event during the 4 weeks following formulation switch. Four patients (2 receiving each formulation) required an increase in dose during the 4 weeks following overnight switch to the alternative formulation.[28,49,51,52]

When switching between IR *Requip* and *Requip XL*, the initial switching dose of IR *Requip* or *Requip XL* was the dose that most closely matched the total daily dose of the other formulation. Following overnight direct conversion patients were then titrated as necessary based on therapeutic response and tolerability. It was recommended that the daily dose be administered in the morning or at the same time each day.

Switching Between Pramipexole and Requip XL

Study Description

A three-arm, open-label study examined overnight switching of patients with Parkinson's disease (PD) (N=60) stabilized on pramipexole to *Requip XL*.[31] Patients with prior exposure to *Requip XL* or current use of immediate-release (IR) *Requip* were excluded. Twenty patients each were switched overnight to *Requip XL* at milligram ratios of 1:3, 1:4 or 1:5 (pramipexole:*Requip XL*) according to the conversions shown in Table 4. The goal of the treatment switch study was comparable symptom control without adverse events. Patients were followed for 1 month after initiation of treatment with *Requip XL*.

Table 4. Doses for Conversion of Pramipexole to *Requip XL*

	1:3 Conversion Ratio		1:4 Conversion Ratio		1:5 Conversion Ratio	
Total Dose* Pramipexole	**Actual Dose* *Requip XL***	**Calculated Ratio Dose*† *Requip XL***	**Actual Dose* *Requip XL***	**Calculated Ratio Dose*† *Requip XL***	**Actual Dose* *Requip XL***	**Calculated Ratio Dose*† *Requip XL***
0.375	2	1.125	2	1.5	2	1.875
0.75	2	2.25	4	3	4	3.75
1.5	4	4.5	6	6	8	7.5
2.25	6	6.75	8	9	12	11.25
3	8	9	12	12	16	15
3.75	12	11.25	16	15	20	18.75
4.5	16	13.5	20	18	24	22.5

Requip XL tablet strengths: 2 mg, 4 mg, 8 mg, and 12 mg

* mg/day

† Calculated ratio doses of *Requip XL* were rounded to the nearest available tablet strengths of *Requip XL*

After switching from pramipexole to *Requip XL*, patients were assessed during the first 5 working days of treatment, thereafter which adjustments in dosage (in 2 mg to 4 mg increments up to a maximum dose of 24 mg/day) of *Requip XL* were allowed to maintain efficacy or reduce adverse events. Patient demographics and patient characteristics were similar between treatment groups and included the following (values are means): patient age - 65 years; disease duration - 8 years; pramipexole dose - 2.4 mg/day; Hoehn & Yahr stage - 2.2; Unified Parkinson's Disease Rating Scale (UPDRS) Motor score - 23.

Study Results

Seventy-eight percent of patients (47/60) completed the study. Seventy percent (33/47) of these patients preferred *Requip XL* for one or more of these reasons: convenient once-daily dosing, reduced somnolence, reduced edema and reduced "off" time. Fewer patients required discontinuation of therapy in the 1:4 conversion ratio group (10%) versus the 1:3 (30%) and 1:5 (25%) conversion groups. In addition, 65% of patients in this group required no further dosage adjustment after conversion. Approximately 20% and 50% of patients in the 1:3 and 1:5 conversion groups, respectively, required changes in dosage (if symptoms were inadequately controlled or patients experienced adverse events).of *Requip XL* after conversion from pramipexole.

The majority of adverse events were typical of dopamine agonist therapy, were mild, and resolved with dose adjustments. See Table 5 for a list of adverse events reported during the study. Adverse events occurring in ≥ 5% of patients regardless of medication preference were Parkinson's Disease worsening (35%), dizziness (18%), nausea (13%), and sleepiness (15%).

Table 5. Adverse Events Reported By Patient Preference During the Study

Adverse Event	Preferred *Requip XL* (n=33) n (%)	Preferred Pramipexole (n=14) n (%)	Discontinued Conversion Treatment (n=13) n (%)	Adverse Event Regardless of Patient Preference (n=60) n (%)
Parkinson's Disease worsening	6 (18)	8 (57)	7 (54)	21 (35)
Dizziness	5 (15)	3 (21)	3 (23)	11 (18)
Nausea	5 (15)	3 (21)	0	8 (13)
Sleepiness	4 (12)	2 (14)	3 (23)	9 (15)
Anxiety	2 (6)	0	0	2 (3)
Constipation	1 (3)	0	0	1 (2)
Diarrhea	1 (3)	0	1 (8)	2 (3)
Edema	1 (3)	1 (7)	0	2 (3)

Adverse Event	Preferred *Requip XL* (n=33) n (%)	Preferred Pramipexole (n=14) n (%)	Discontinued Conversion Treatment (n=13) n (%)	Adverse Event Regardless of Patient Preference (n=60) n (%)
Headache	1 (3)	0	0	1 (2)
Heartburn	1 (3)	0	0	1 (2)
Insomnia	1 (3)	0	1 (8)	2 (3)
Weakness	1 (3)	0	0	1 (2)
Disorientation	0	0	1 (8)	1 (2)
Dyskinesia	0	1 (7)	1 (8)	2 (3)
Fatigue	0	1 (7)	0	1 (2)
Increased time spent "off"	0	0	1 (8)	1 (2)
Leg cramps	0	1 (7)	0	1 (2)
Slow kick-in	0	1 (7)	0	1 (2)

There were no significant changes in UPDRS scores, PDQ-39 quality of life assessment scores or Epworth Sleepiness Scale scores conducted at baseline and 1 month after switching, regardless of patient preference.

The authors concluded that the most effective initial conversion ratio was 1:4 pramipexole:*Requip XL*with additional adjustments in dose as needed to improve efficacy and tolerability. Large, well controlled, clinical trials have not been conducted to evaluate the optimal method for switching patients from pramipexole to *Requip XL* making it difficult to recommend switching guidelines that are suitable for all patients. It is therefore recommended that the switching regimen be based on clinical judgment of the healthcare professional with individualization for each patient.

5. EFFICACY AND SAFETY TRIALS

5.1 *Requip XL* vs. IR *Requip* for PD (Adjunct Therapy)

Study Description

The PREPARED Study (**P**rolonged **R**elease ropinirol**E** in **PAR**kinson's diseas**E** Stu**D**y) was a 24-week, randomized, double-blind, parallel group study that compared adjunctive *Requip XL* and IR *Requip* in patients with advanced Parkinson's disease (PD) not optimally controlled on L-dopa. *Requip XL* administered once daily (2-24 mg/day) was compared to IR *Requip* three times daily (0.75-24 mg/day).[21,22,23,24,25,26] A forced up-titration of dose occurred over the first 4 weeks (minimum 8 mg/day *Requip XL* or 3 mg/day IR *Requip*), after which the dose was adjusted according to the investigator's clinical judgement. The L-dopa dose was reduced after patients reached a reduction in baseline awake time spent "off" of ≥ 1.5 hours.

Study Results

Baseline Patient Demographics

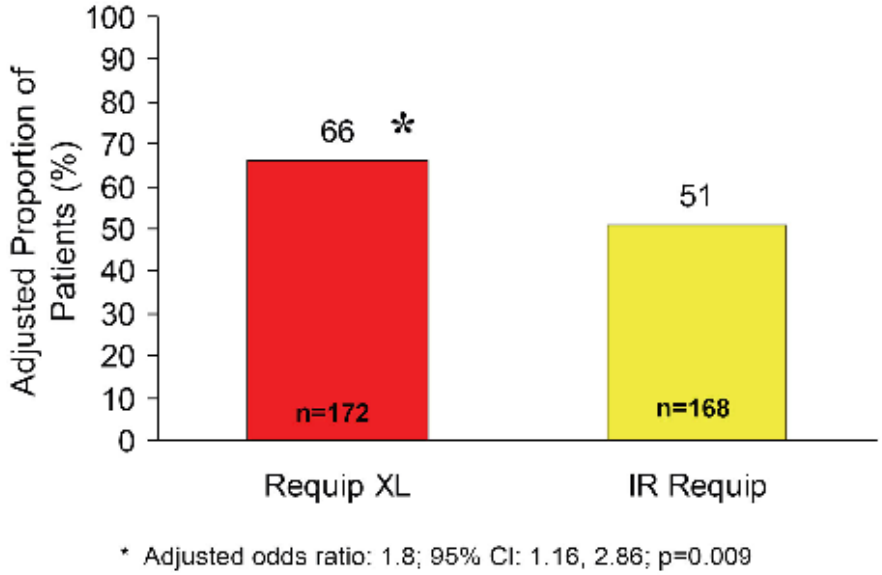
A total of 350 patients were randomized (*Requip XL*, N=177 and IR *Requip*, N=173), of which 167 (48%) completed all 24 weeks of the study. Patient demographics and baseline characteristics were similar between treatment groups. The mean age was 65 years and the mean disease duration was 7.7 years. The majority of patients had a Hoehn & Yahr stage of II-III. The average duration of L-dopa use was 5.5 years.

Efficacy

The adjusted proportion of patients maintaining a ≥ 20% reduction in "off" time over two consecutive visits (maintained reduction) at Week 24 (primary endpoint) at the doses attained in this study was significantly greater in the intent-to-treat (ITT) population receiving *Requip XL* (66%, 110/172) vs. IR *Requip* (51% (85/168) [adjusted odds ratio: 1.8; *P*=0.009; week 24 (Last Observation Carried Forward =LOCF]. See Figure 3.

Numerical trends in favor of *Requip XL* were seen as early as week 2 (the first timepoint when this endpoint was assessed) and were maintained throughout the rest of the 24 week treatment period.

Figure 3. Adjusted Proportion of Patients with ≥ 20% Maintained Reduction in Daily Awake Time "Off" at Week 24 (LOCF)



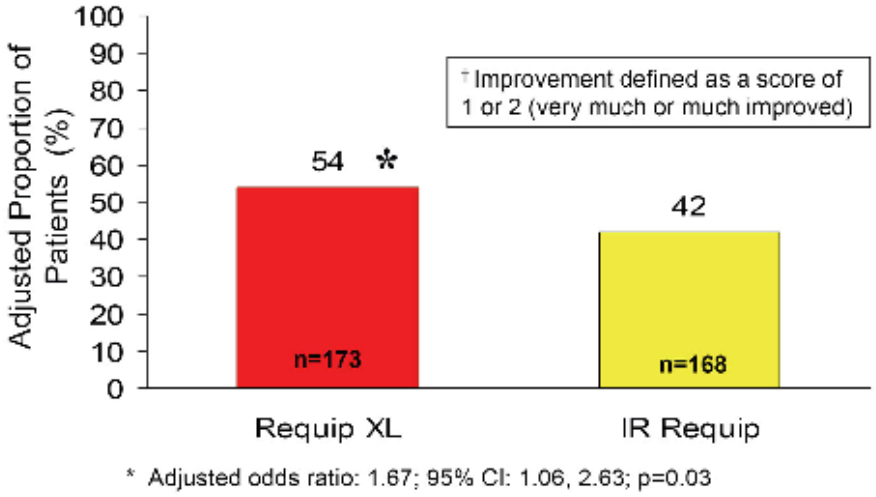
A high proportion of protocol violators warranted a post-hoc assessment of the effects of *Requip XL* and IR *Requip*. The per protocol (PP) population comprised only those patients who had reduced their L-dopa dose as specified in the protocol (N=167). A failure to reduce the L-dopa dose at the mandated visit was the most common reason for protocol violations.

In the PP population, the proportion of patients maintaining a ≥ 20% reduction in "off" time over two consecutive visits at Week 24 was also significantly greater for *Requip XL* (60%, 48/80) vs. IR *Requip* (40%, 35/87) [adjusted odds ratio: 2.8;95% CI: 1.38, 5.59; *P*=0.004].

At week 24 (LOCF), the mean (SD) doses were *Requip XL* 18.6 (6.5) mg/day vs. IR *Requip* 10.4 (6.4) mg/day (ITT population). Due to the faster up-titration schedule for *Requip XL* compared to IR *Requip* and the fact that patients were progressed through the dose levels at the same rate, patients reached higher doses in a shorter time on *Requip XL*. At baseline the L-dopa doses were 685 mg/day for patients receiving *Requip XL* and 659 mg/day for patients receiving IR *Requip*. The mean reductions from baseline in L-dopa dose (ITT population) were *Requip XL* -162 (226) mg vs. IR *Requip* -113 (138) mg.

In the ITT population, there was a statistically significant increase in the adjusted proportion of patients with much or very much improvement on the CGI-I scale for *Requip XL* when compared to IR *Requip* (*Requip XL* (54%, 95/173) vs. IR *Requip* (42% (73/168) [adjusted odds ratio: 1.7; 95% CI: (1.06, 2.63), *P*=0.03; week 24 LOCF]) and mean adjusted change from baseline in UPDRS total motor score with patients in an "on" state (*Requip XL* (-10.2) vs. IR *Requip* (-7.9) [adjusted treatment difference: -2.3; 95% CI: -4.27, -0.33), *P*=0.02; week 24 LOCF]). See Figure 4.

Figure 4. Adjusted Proportion of Patients with Improved† CGI-I Scale Score at Week 24 (LOCF)



While there were numerical trends in favor of *Requip XL*, there was no statistically significant difference between *Requip XL* and IR *Requip* for the mean change from baseline in the following: percent awake time spent "off", ADL scores with patients in an "on" or "off" state, and Parkinson's Disease Sleep Scale (PDSS) total score.

Safety Results

Adverse events reported by > 5% of patients treated with *Requip XL* while on treatment are summarized in Table 6. The number of patients reporting down-titration adverse events, serious adverse events and adverse events leading to withdrawal were similar for patients receiving *Requip XL* vs. IR *Requip*.

Table 6. Adverse Events (AEs) for *Requip XL* and IR *Requip*

	Percent (%) of Patients	
	***Requip XL* (n=177)**	**IR *Requip* (n=173)**
Nausea	15	18
Dyskinesia	11	6
Dizziness	10	6
Somnolence	7	6
Hallucination	7	2
Fatigue	7	7
Headache	6	6
Abdominal Pain	6	6
Insomnia	6	6

5.2 *Requip XL* as Adjunctive Treatment of PD

EASE PD Adjunct Study

Study Description

The EASE-PD Adjunct study was a multi-center, double-blind, placebo-controlled trial designed to assess the efficacy and safety of *Requip XL* in patients with PD not optimally controlled by L-dopa therapy.[27] Patients were randomized (1:1) to receive once-daily *Requip XL* (n=202) or placebo (n=191), in addition to L-dopa, for 24 weeks.

All patients had a diagnosis of idiopathic PD (Hoehn & Yahr stage II–IV), a minimum of 3 hours awake time spent "off" during the placebo run-in period, and suboptimal control with L-dopa-only therapy. Patients must also have been receiving a stable dose of L-dopa for at least 4 weeks prior to screening.

From a starting dose of *Requip XL* 2 mg/day, dose titration was performed until an optimal therapeutic dose was achieved, up to a maximum of 24 mg/day or adverse events occurred; all patients were titrated to at least 6 mg/day. When patients reached a dose of 8 mg/day, and with each subsequent increase in study medication, a corresponding reduction in L-dopa dose (by one half or one whole tablet) was required. If loss of symptom control occurred with the reduction in L-dopa, then the dose of *Requip XL* was increased to the next level with no adjustment in L-dopa dose. Patients who did not experience improvement in symptoms following two up-titrations of *Requip XL* could have their L-dopa dose increased up to, but not exceeding, baseline levels.

Please note, the dosing for *Requip XL* in this study differs from the approved prescribing information for *Requip XL*.

Primary Endpoint

The primary endpoint of the study was the mean change from baseline in awake time (hours) spent "off" at Week 24 (LOCF) as measured by patient diaries. "Off" state was described as a lack of mobility and a return of Parkinson's disease symptoms when Parkinson's disease medication was no longer working. Additional details of the study design and dosage regimen may be found in the published paper.[27]

Secondary Endpoints

The study included the following secondary endpoints: mean change from baseline in the hours of "on" time, percentage of "on " time, percentage of "off" time, hours of "on" time without troublesome dyskinesia, percentage of "on" time without troublesome dyskinesia, mean change from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS) Motor score (part III), UPDRS Activities of Daily Living (ADL) score (part II), Beck Depression Inventory-II (BDI-II), Parkinson's Disease Quality of life questionnaire (PDQ-39) subscore, Epworth Sleepiness Scale (ESS), Parkinson's Disease Sleep Scale (PDSS), Clinical Global Impression-Improvement scale score of "very much improved" or "much improved," proportion of patients requiring an increase in L-dopa dose after it was decreased, time to reinstatement of L-dopa after previous dose increase, and the proportion of responders (responders were defined as those patients having at least a 20% reduction from baseline in "off" time and at least a 20% reduction from baseline in L-dopa dose). "On" state was defined as the period of time when the Parkinson's disease medication was providing benefit. Troublesome dyskinesia was described as involuntary movements that created discomfort or interfered with functioning.

Patient Demographics

Patient baseline characteristics were similar between treatment groups. See Table 7. The percentage of patients who completed the study were 83% receiving *Requip XL* and 70% receiving placebo group. At Week 24 (LOCF), the mean (standard deviation) dose of *Requip XL* was 18.8 (6.3) mg/day and 20 (5.6) mg/day for matching placebo.

Table 7. Patient Baseline Characteristics

	Requip XL **(n=201)**	**Placebo (n=190)**
Age (y)	66.3 (9.2)	66 (9.7)
Women, n (%)	84 (42)	61 (32)
Age at onset of PD (y)	57.6 (10.5)[f]	57.3 (10.7)[c]
Duration of PD (y)	8.6 (4.8)[a]	8.6 (5.2)[e]
Hoehn & Yahr stage	2.7 (0.5)	2.7 (0.6)
Duration of L-dopa (y)	6.5 (4.4)[a]	6.6 (4.3)[e]
Baseline L-dopa dose (mg/day)	824 (424)[a]	776 (357)
Baseline total time "off" (hours)	7.0 (2.8)	7.0 (2.6)
Baseline UPDRS motor score*	29.8 (12.9)[b]	30.7 (14.4)[c]

All values are mean (SD) unless stated otherwise.

[a]n=199; [b]n=197; [c]n=188; [d]n=198; [e]n=187; [f]n=200.

*Range 0–108, where 0=normal/no symptoms, and 108=worst possible case; assessed at least 2 hours post-L-dopa dose.

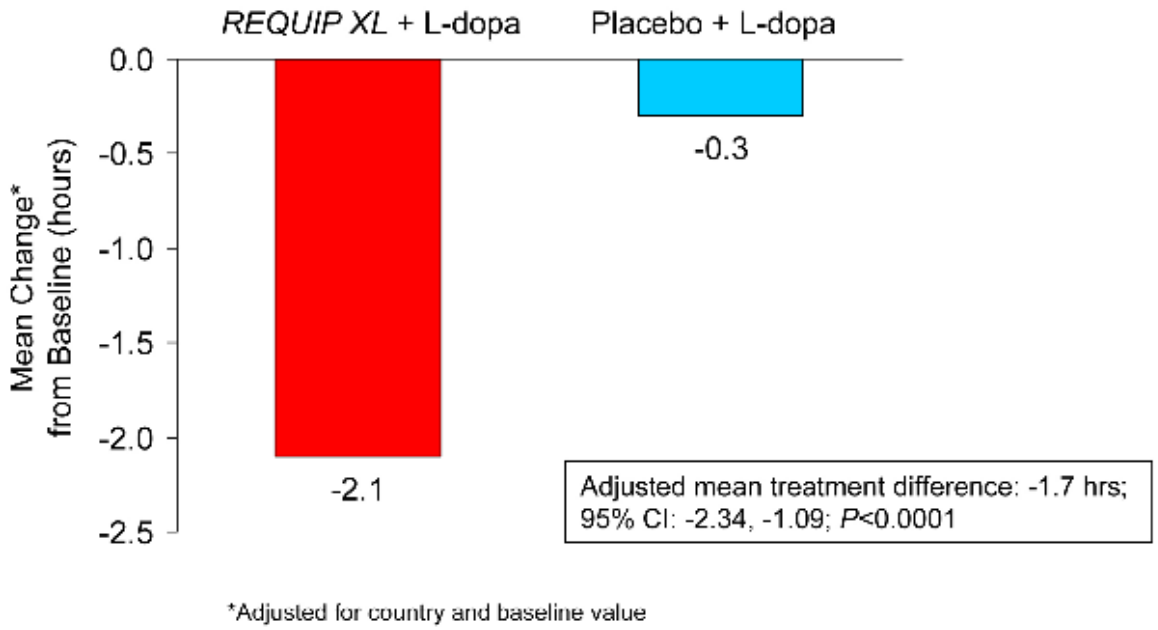
SD=standard deviation; UPDRS=Unified Parkinson's Disease Rating Scale; y=years.

There were 34 patients taking *Requip XL* and 57 patients taking placebo discontinued study drug before study completion. Lack of efficacy was the most common reason for discontinuation with 3% (6/202) and 14% (27/191) discontinuing for this reason for patients receiving *Requip XL* and placebo, respectively.

Primary Endpoint Results

Baseline measurements for "off" time were approximately 7 hours in each treatment group.[27] At week 24, mean change from baseline in "off" time was -2.1 hours for patients receiving *Requip XL* and -0.3 hours for those receiving placebo. See Figure 5. The adjusted mean treatment difference between *Requip XL* and placebo was -1.7 hours (95% CI: -2.34, -1.09; *P* <0.001). This statistical benefit for *Requip XL* was observed at all measured time points in the study from week 2 to week 24.

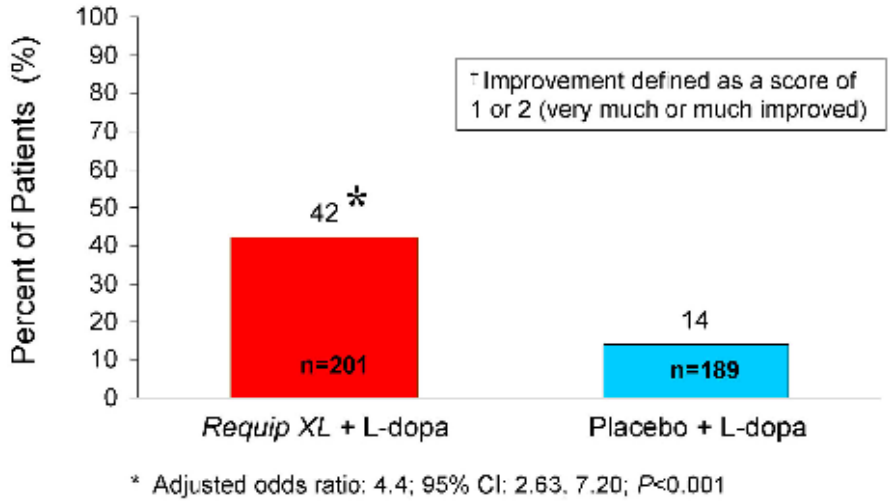
Figure 5. Mean Change* from Baseline in Awake Time Spent "Off" at Week 24 (LOCF)



Secondary Endpoint Results

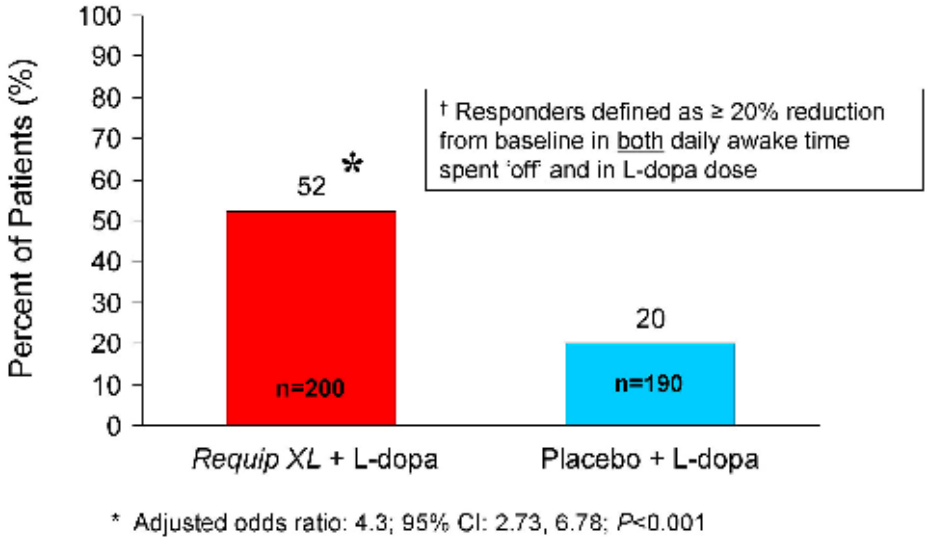
Forty-two percent (83/200) of patients receiving *Requip XL* were considered responders on the CGI-I scale at week 24 versus 14% (27/189) of patients in the placebo group (OR: 4.4; 95% CI: 2.63, 7.20; *P* <0.001). See Figure 6.

Figure 6. Percent of Patients with Improved† CGI-I Scale Score at Week 24 (LOCF)



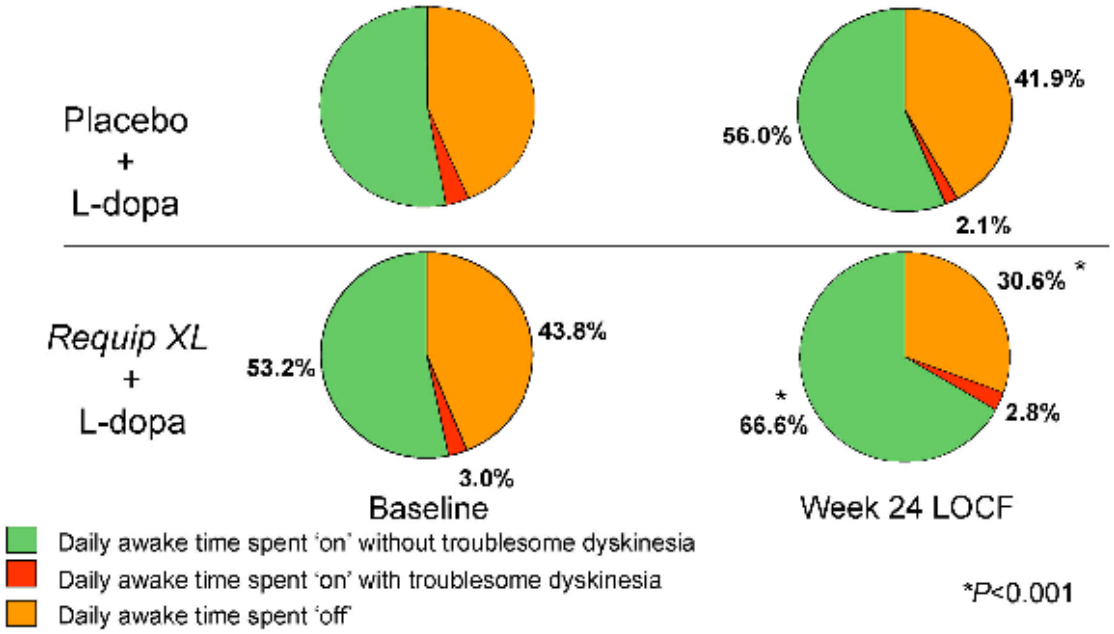
In regards to the endpoint of 20% reduction in "off" time and 20% reduction in L-dopa dose, 52% (103/200) of patients receiving *Requip XL* and 20% (38/190) of patients receiving placebo were considered responders (OR 4.3; 95% CI: 2.73, 6.78; *P* <0.001). See Figure 7.

Figure 7. Percent of Responders† at Week 24 (LOCF)



The following secondary endpoints were also statistically significant for patients receiving *Requip XL* versus placebo: hours of "on" time, hours of "on" time without troublesome dyskinesia, percent of "off" time, percent of "on" time, percent of "on" time without troublesome dyskinesia. See Figure 8.

Figure 8. Daily Percent of "Off" Time, "On" Time, and "On" time with and without Troublesome Dyskinesia



UPDRS total motor scores and UPDRS activities of daily living (ADL) scores were also statistically significant for patients receiving *Requip XL* versus placebo. See Figure 9 and Figure 10.

Figure 9. Mean Change* from Baseline in UPDRS Total Motor Score at Week 24 (LOCF)

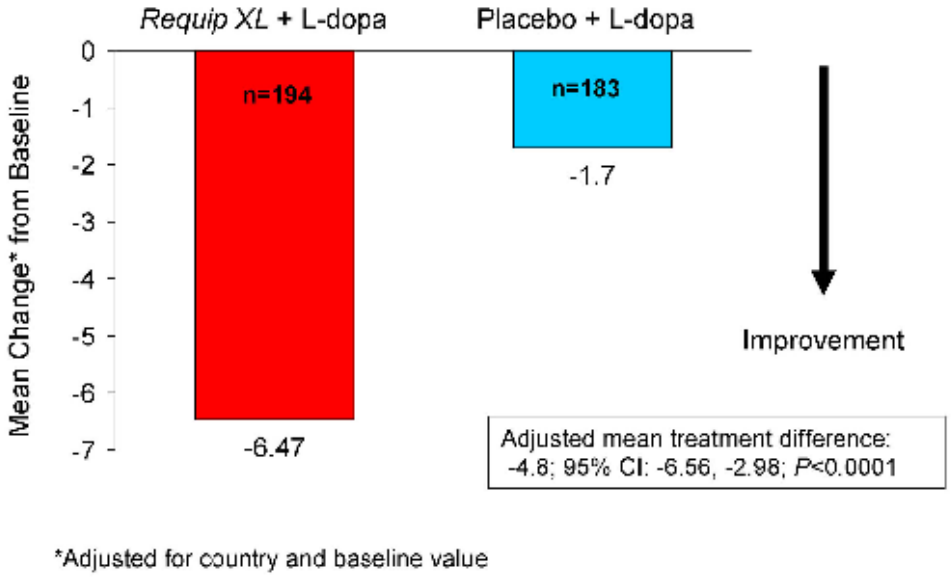
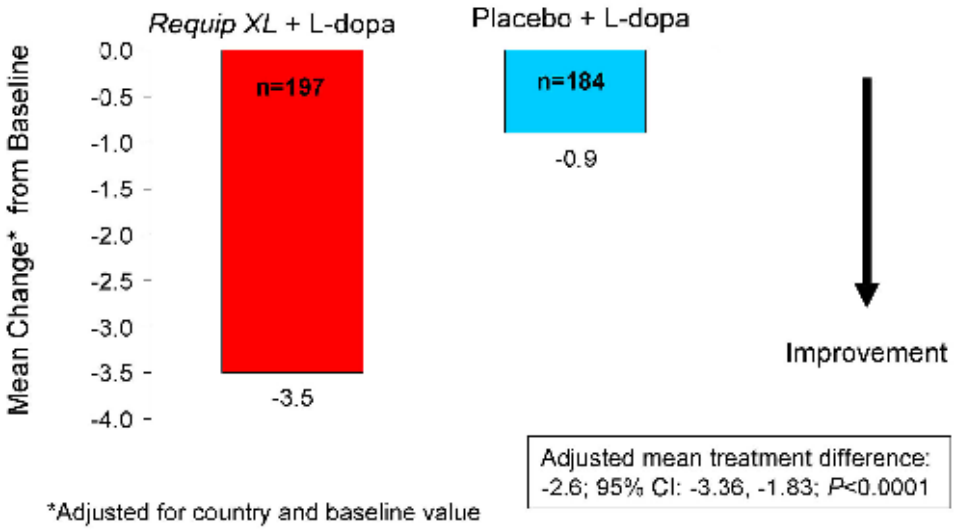


Figure 10. Mean Change* from Baseline in Total ADL Score at Week 24 (LOCF)

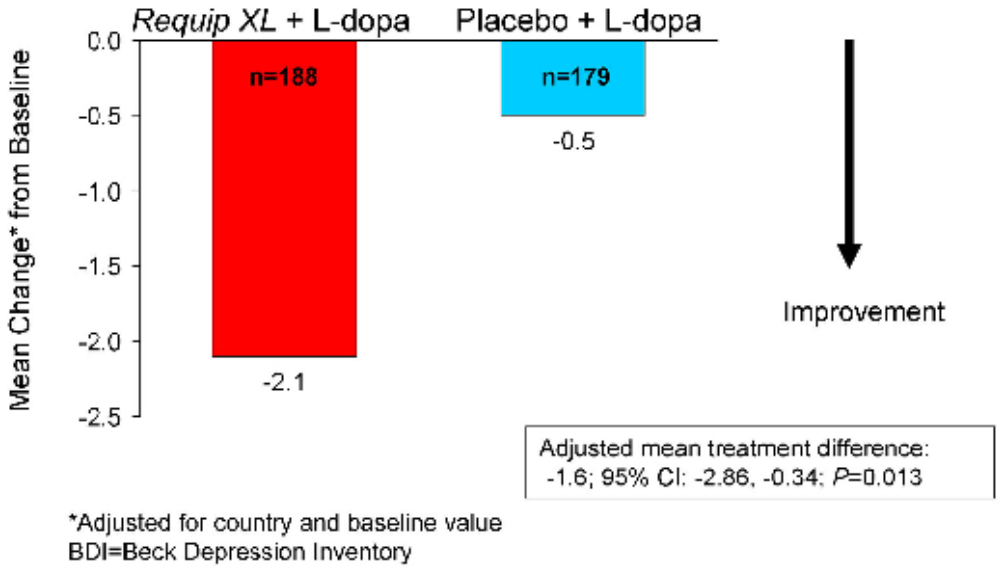


The mean dose of L-dopa for patients treated with *Requip XL* was 546 (± 378) mg/day and 613 (± 349) mg/day in those treated with placebo at week 24. This represented a mean decrease of 278 (± 193) mg/day and 164 (± 164) mg/day of L-dopa for those receiving *Requip XL* and placebo, respectively. For patients receiving *Requip XL*, 7% (14/191) of patients required reinstatement of L-dopa after dose reduction was attempted. This number was 28% (49/174) in the placebo group (OR: 0.2; 95% CI: 0.09, 0.34; *P* <0.001). Time to reinstatement of L-dopa was also significantly different for patients receiving *Requip XL* versus placebo in favor of active drug (*P* <0.0001).

Depression Endpoint Results

The Beck Depression Inventory II (BDI-II) is a 21-item questionnaire that describes different aspects of mood and assesses general depression. Each item has four possible responses, rated 0 (least severe) to 3 (most severe), for a maximum total score of 63.[53,54] Mean BDI-II total scores at baseline, were approximately 16 in each treatment group. There was a statistically significant treatment difference in favor of *Requip XL* compared with placebo for mean change from baseline in BDI-II score at Week 24 (LOCF, *P* = 0.0130; See Figure 11).

Figure 11. Mean Change* from Baseline in BDI-II Total Score at Week 24 (LOCF)

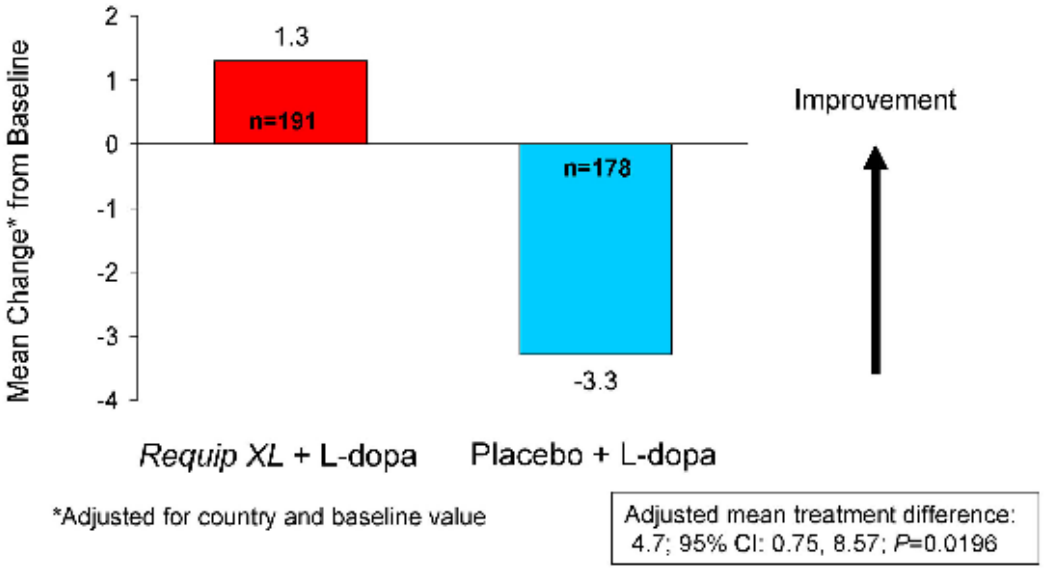


*Adjusted for country and baseline value
BDI=Beck Depression Inventory

Sleep Endpoint Results

Mean Parkinson's Disease Sleep Scale (PDSS) total score and mean Epworth Sleepiness Scale (ESS) total scores were similar between treatment groups at baseline.[54,55] At Week 24 (LOCF), *Requip XL* significantly reduced the symptoms of sleep disturbance, compared with placebo, as measured by the change from baseline in PDSS total score (*P*=0.0196) (See Figure 12). There was no difference observed for *Requip XL* and placebo for the change from baseline in daytime somnolence at Week 24 (LOCF), as measured by ESS total score (*P*=0.3692).

Figure 12. Mean Change* from Baseline in PDSS Total Score at Week 24 (LOCF)



Quality of Life Endpoint Results

The Parkinson's Disease Quality of Life questionnaire (PDQ-39) covers eight dimensions of health that are reported as adversely affected by patients with PD on a scale of 0–100, where 0=no problem and 100=maximum level of problem.[53,54] Baseline mean PDQ-39 summary index scores were well matched for the two treatment groups. At Week 24 (LOCF), there was a significant improvement in PDQ-39 summary index score: adjusted mean change (SE) from baseline was –2.6 (1.04) in the group receiving *Requip XL* versus 0.9 (1.08) for placebo (95% CI: –5.5, –1.4; $P = 0.001$). The group receiving *Requip XL* also reported significant treatment benefit, compared with the placebo group, in the change from baseline in the mobility, activities of daily living, emotional well-being, stigma, and communication domains of the PDQ-39 at Week 24 (LOCF; See Table 8). Change from baseline to Week 24 (LOCF) was similar for the two treatment groups for the social support, cognitive impairment, and bodily discomfort domains of the PDQ-39.

Table 8. Adjusted Analyses of Change from Baseline in the Domains of the PDQ-39 (Modified ITT Population)*

Domain	*Requip XL*: Adjusted mean change from baseline	Placebo adjusted mean (SE) change from baseline	Adjusted treatment difference (95% CI)	*P* value
Mobility	–4.9 (1.7), n=186	1.9 (1.7), n=172	–6.8 (–10.1, –3.5)	<0.0001†
ADL	–5.4 (1.7), n=185	1.1 (1.7), n=176	–6.5 (–9.7, –3.3)	<0.0001†
Emotional well-being	–4.3 (1.5), n=182	–0.6 (1.5), n=172	–3.7(–6.7, –0.8)	0.0124†
Stigma	–3.3 (1.8), n=187	1.2 (1.9), n=178	–4.5 (–8.1, –0.9)	0.0150†
Social support	–1.5 (1.5), n=185	–0.3 (1.5), n=177	–1.2 (–4.1, 1.8)	0.4385
Cognitive impairment	3.4 (1.3), n=188	2.9 (1.3), n=178	0.5 (–2.1, 3.1)	0.7176
Communication	–1.4 (1.6), n=187	2.4 (1.7), n=176	–3.7 (–6.9, –0.6)	0.0193†
Bodily discomfort	–3.6 (1.7), n=189	–1.5 (1.8), n=176	–2.1 (–5.4, 1.3)	0.2224

For all domains, a decrease from baseline indicates an improvement.

*Adjusted for country and baseline score. † statistically significant.

ADL=activities of daily living; CI=confidence interval; ITT=intention-to-treat; PDQ-39=Parkinson's Disease Quality of Life questionnaire; SE=standard error.

Post-Hoc Anaylsis – Tremor, Rigidity and Bradykinesia

At baseline, UPDRS (Part III) total motor scores were similar between treatment groups (29.8 *Requip XL* vs. 30.7 placebo). There was a statistically significant improvement (reduction) in UPDRS total motor score for patients receiving *Requip XL* compared with patients receiving placebo at both Week 4 (observed cases) and Week 24 (LOCF). At week 24, mean change from baseline in UPDRS total motor score was -6.5 for patients receiving *Requip XL* and -1.7 for those receiving placebo. The adjusted mean treatment difference between *Requip XL* and placebo was -4.8 (95% CI: -6.56, -2.98; $P < 0.0001$).

At baseline, UPDRS scores for the tremor, rigidity and bradykinesia components were similar between treatment groups. See Table 9.

Table 9. Patient Baseline UPDRS Scores

	Requip XL **(n=201)**	**Placebo (n=190)**
Baseline UPDRS items associated with tremor (items 20 and 21)	3.8 (3.7)[c]	4.4 (4.1)[b]
Baseline UPDRS items associated with rigidity	6.2 (3.5)[a]	6.2 (3.7)[d]
Baseline UPDRS items associated with bradykinesia (items 23–26)	11.1 (5.2)[c]	10.7 (5.3)[b]

All values are mean (SD) unless stated otherwise.

[a]n=197; [b]n=188; [c]n=198; [d]n=187.

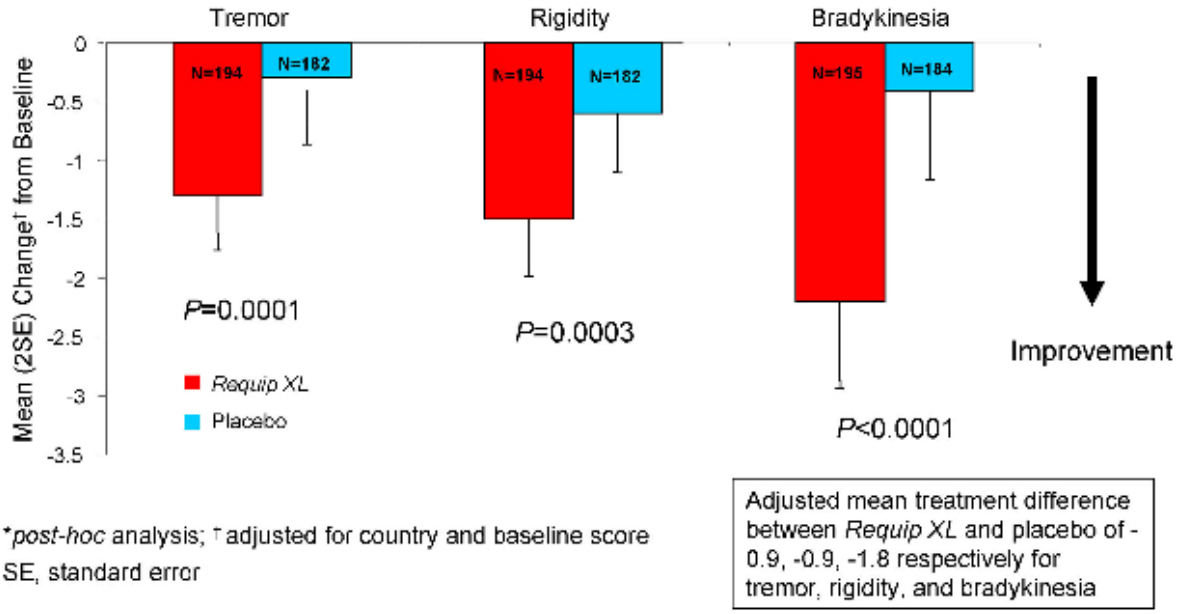
*Range 0–108, where 0=normal/no symptoms, and 108=worst possible case; assessed at least 2 hours post-L-dopa dose.

SD=standard deviation; UPDRS=Unified Parkinson's Disease Rating Scale.

Post-Hoc Analysis Results

A post-hoc analysis assessed the mean change from baseline in the tremor (items 20 and 21), rigidity (item 22) and bradykinesia (items 23-26) components of the UPDRS motor examination at Week 24 (LOCF).[56] There was a statistically significant improvement (reduction) in UPDRS score for the tremor, rigidity and bradykinesia components of the UPDRS for patients receiving *Requip XL* compared with patients receiving placebo at Week 24 (LOCF). See Figure 13.

Figure 13. Mean Change† from Baseline in the Tremor, Rigidity, and Bradykinesia Components of the UPDRS Motor Examination at Week 24 (LOCF)*



For tremor the adjusted mean treatment difference between *Requip XL* and placebo was -0.9 (95% CI: -1.3, -0.4; $P = 0.0001$). For rigidity the adjusted mean treatment difference between *Requip XL* and placebo was -0.9 (95% CI: -1.4, -0.4; $P = 0.0003$). For bradykinesia the adjusted mean treatment difference between *Requip XL* and placebo was -1.8 (95% CI: -2.5, -1; $P < 0.0001$).

Safety Results

The safety population consisted of 393 patients who were randomized and received at least one dose of study medication. This included 202 patients who received *Requip XL* and 191 patients who received placebo. Sixty-four percent (129/202) and 55% (106/191) of patients receiving *Requip XL* and placebo, respectively, reported adverse events. The most commonly reported adverse events are listed in Table 10.

Table 10. Adverse Events (AEs) and Withdrawal Rates for *Requip XL* and Placebo

	Number of Patients (%)	
	***Requip XL* + L-dopa (n=202)**	**Placebo + L-dopa (n=191)**
Patients with at least one AE	129 (64)	106 (55)
Dyskinesia	27 (13)	5 (3)
Nausea	23 (11)	7 (4)
Dizziness	16 (8)	6 (3)
Somnolence	14 (7)	7 (4)
Hallucinations	12 (6)	2 (1)
Orthostatic hypotension	11 (5)	3 (2)
Serious AEs	8 (4)	7 (4)
Withdrawal due to on-treatment AEs	11 (5)	10 (5)

During the 7-day down-titration phase, which occurred at the end of the study or upon patient discontinuation, adverse events indicating withdrawal symptoms were not evident. Five percent of patients in both treatment groups withdrew from the study due to adverse events. Hallucinations led to withdrawal of 4 patients (2%) receiving *Requip XL* and 2 patients (1%) receiving placebo. Nausea led to withdrawal of 2 patients (1%) receiving *Requip XL* and 1 placebo-treated patient (<1%). Worsening of parkinsonism led to withdrawal of 0 patients treated with *Requip XL* and 2 patients (1%) receiving placebo. Adverse events classified as serious were reported by 4% of patients in each treatment group. Serious adverse events considered to be medication-related by the investigator were syncope and hallucinations for patients treated with *Requip XL*.

The majority of adverse events were mild to moderate in nature. Dyskinesia and nausea, reported by greater than 10% of patients receiving *Requip XL*, were reported during the first 4 weeks of the study. This 4-week period included the up-titration of study drug, before planned reduction of L-dopa dose. In terms of hallucinations and unintended sleep episodes, 16 (8%) patients receiving *Requip XL* reported hallucinations (with 4 of these patients discontinuing the study) and 1 patient reported an unintended sleep episode (this patient remained in the study). The authors concluded that *Requip XL* was safe and well-tolerated as adjunctive treatment to L-dopa in patients with Parkinson's disease.

5.3 *Requip XL* as Monotherapy Treatment of PD

EASE PD Monotherapy Study

Study Description

Per European regulatory requirements, the EASE-PD Monotherapy study was a 36-week, multi-center, randomized, double-blind, double-dummy, three-period, two-treatment, non-inferiority, crossover study designed to compare the efficacy and safety of once daily *Requip XL* to IR *Requip* three times daily in patients with early Parkinson's disease.[28,49,50] Following a 1-week placebo run-in period, there were four phases of the study: a 12-week titration period and three 8-week maintenance treatment periods, for a total duration of 36 weeks. After a 1-week placebo run-in period, patients were randomized (1:1:1:1) to one of four formulation sequences as follows:

- *Requip XL* - *Requip XL* - IR *Requip*
- *Requip XL* - IR *Requip* - IR *Requip*
- IR *Requip* - IR *Requip* - *Requip XL*
- IR *Requip* - *Requip XL* - *Requip XL*

Patients entered a 12-week titration period with the first formulation in their sequence. Half of the patients started titration with *Requip XL* and half with IR *Requip*. At the end of the 12-week titration period,

patients who achieved a stable Unified Parkinson's Disease Rating Scale (UPDRS) motor score (defined as no more than a 2-point change between weeks 10 and 12) entered the first 8-week flexible-dose maintenance period. In flexible-dose maintenance period 1, patients continued to receive the formulation they had received during the titration period. At the end of flexible-dose maintenance period 1, half the patients underwent overnight switching to the closest dose of the alternative formulation of IR *Requip*, with the other half receiving a dummy switch. See Table 11. At the end of the second 8-week flexible-dose maintenance period, the remaining half of patients underwent overnight switching, with the other half receiving a dummy switch. Thus, by flexible-dose maintenance period 3, all patients had switched to the opposite formulation. Dose adjustments were permitted during the first 4 weeks of each flexible-dose maintenance period.

Table 11. - See Appendix

Dosing

Patients randomized to *Requip XL* received doses from 2 to 24 mg/day. The starting dose was 2 mg/day. Overall, a total of eight dose levels were available (2, 4, 6, 8, 12, 16, 20 and 24 mg/day). If possible, patients received weekly fixed-dose titration (based on tolerability) over the first four weeks to a dose of *Requip XL* 8 mg/day (Dose Level 4). Further dose titration was dependent on the response/tolerance of each individual patient.

Requip XL taken once daily was compared with IR *Requip* (0.75 to 24 mg/day) taken in three divided doses. IR *Requip* was administered per approved product labeling and had a starting dose of 0.75 mg/day and patients were then titrated to an optimal therapeutic response. Overall, a total of 13 dose levels were available (0.75, 1.5, 2.25, 3, 4.5, 6, 7.5, 9, 12, 15, 18, 21 and 24 mg/day). If possible, patients were titrated to Dose Level 4 (3 mg/day) over the first four weeks. Further dose titration was dependent on the response/tolerance of each individual patient.

Please note, the dosing for *Requip XL* in this study differs from the approved prescribing information for *Requip XL*.

Baseline Patient Demographics

A total of 161 patients were randomized, of which 123 (76%) patients completed all 36 weeks of the study. There was an equal distribution of males and females. The mean age was 60.3 years and the mean disease duration was 2.7 years. Majority of the patients had a Hoehn & Yahr stage of I-II. UPDRS motor and ADL, BDI, ESS and PDSS scores were similar for both treatment group.

Primary Endpoint Results

The primary efficacy endpoint was the mean change between period baseline and endpoint in UPDRS total motor score, reported individually for each maintenance period and as an overall score for the three maintenance periods for each formulation.

After initial titration, both treatment groups showed little change from period baseline in UPDRS total motor score over the subsequent flexible-dose maintenance periods. See Table 12. Overall mean (SE) change from period baseline was –0.1 (0.28) for *Requip XL*, and 0.6 (0.3) for IR *Requip*; adjusted treatment difference was –0.7 (95% CI: –1.51, 0.1; $P = 0.0842$). The upper limit of the 95% CI was less than the predefined threshold of 3 points, therefore *Requip XL* was shown to be non-inferior to IR *Requip*. Patients in both treatment groups had a marked improvement (decrease) in mean UPDRS total motor score between study baseline and the end of dose titration before entering the first flexible-dose maintenance period. The mean change was slightly greater for *Requip XL* -10.4 (6.1), than for IR *Requip,* -8.9 (5.9), but this difference was not clinically meaningful.

Table 12. - See Appendix

Secondary Endpoint Results

Results for secondary endpoints are summarized in Table 13.

Table 13. - See Appendix

During the titration phase, the proportion of responders who were "very much improved" or "much improved" on the CGI-I scale was greater for patients receiving *Requip XL* than for those receiving IR *Requip*. At week 12, 70% of patients receiving *Requip XL*, compared with 44% of those receiving IR *Requip*, were CGI-I responders (not statistically significant; odds ratio [OR] = 1.85, $P = 0.0761$). This difference between formulations was still seen at the end of flexible-dose maintenance period 1, but declined during the subsequent flexible-dose maintenance periods (when the mean dose of *Requip XL* decreased and that of IR *Requip* increased). Overall, for the whole study, the proportions of responders were 63% for *Requip XL* and 60.1% for IR *Requip*; treatment difference was 2.8 (95% CI: –8.2, 13.9). Although similar proportions of responders were observed for the two formulations, statistical non-inferiority could not be demonstrated; the study was not prospectively powered to demonstrate non-inferiority for this endpoint.

At week 12, 77% of patients receiving *Requip XL*, compared with 66% of patients receiving IR *Requip* achieved a 30% reduction in UPDRS motor score (no significant difference, OR = 1.74, $P = 0.1581$). At the end of each of the flexible-dose maintenance periods, the proportion of patients in each treatment group reaching this endpoint was similar. There was no statistically significant difference between the two formulations for this endpoint (adjusted OR for *Requip XL* compared with IR *Requip* = 0.66, 95% CI: 0.24, 1.80; $P = 0.413$).

Patients in both treatment groups showed an improvement of about 3 points in the mean UPDRS ADL score during the titration phase. After this time, there was little change in this score, and there were no notable differences between the formulations throughout the trial. The overall treatment difference, which adjusted for period, carry-over effect and period baseline score, was 0.0 (95% CI: –0.40, 0.36; $P = 0.9158$).

After the initial up-titration period, there were minor changes in the mean BDI, ESS and PDSS scores with both treatments. In the analysis of covariance, after adjusting for period, carry-over effect and period baseline score, the overall treatment difference for the BDI was 0.0 (95% CI: –0.91, 0.96; $P = 0.9564$); for the ESS it was 0.2 (95% CI: –0.38, 0.72; $P = 0.5520$) and for the PDSS it was 0.6 (95% CI: –2.46, 3.67; $P = 0.6995$). Note: A non-significant difference on ESS indicates no difference in daytime sleepiness.

The median time to maintained response on CGI-I scale for the first 20 weeks of the trial, before switching formulations was 84 days for patients receiving *Requip XL* vs. 140 days for patients receiving IR *Requip* (no significant difference, adjusted HR = 1.18, 95% CI: 0.77, 1.8; $P = 0.4459$).

Safety Results

In the ITT population, compliance was determined by an algorithm for tablets dispensed and returned in relation to the number of days at each dosage level. Patients were considered to be compliant if their tablet compliance was ≥ 80% and ≤ 120% and if they had not missed > 3 consecutive days of treatment. Overall compliance was significantly higher for patients receiving *Requip XL* (97% in each flexible-dose maintenance period) than for IR *Requip* (88–92% in each flexible-dose maintenance period) (OR = 5.3, 95% CI 1.43, 19.86; $P = 0.0131$).

Similar percentages of patients reported adverse events when receiving *Requip XL* (54%) and IR *Requip* (56%) even though patients had a higher starting dose of *Requip XL* (2 once daily) compared to IR *Requip* (0.25 mg three times daily) and reached higher doses of *Requip XL* faster than with IR *Requip*. Adverse events reported by ≥ 5% of patients are listed in Table 14.[28,49,51,52] The most common adverse events were nausea and somnolence for both formulations. These adverse events occurred most frequently during the titration period (regardless of which formulation was being titrated); there were very few new incidences of these adverse events in the final flexible-dose maintenance period. Most of the adverse events were mild or moderate in intensity. Adverse events leading to withdrawal from the study occurred in 5% (n=7) of patients receiving *Requip XL* vs. 6% (n=9) of patients receiving IR *Requip*.

Table 14. Adverse Events (AEs) and Withdrawal Rates for *Requip XL* and IR *Requip* *

	***Requip XL* (n=140)**		**IR *Requip* (n=149)**	
Adverse Event	**Patients with AEs (%)**	**Patient withdrawals due to AEs (%)**	**Patients with AEs (%)**	**Patient withdrawals due to AEs (%)**
Nausea	19	< 1	20	<1
Somnolence	11	0	15	0
Dizziness	6	0	6	0
Headache	6	0	5	0
Constipation	5	0	5	0
* AEs in ≥ 5% of patients in either treatment group				

Adverse events that were severe in intensity were reported by 8 patients (6%) who received *Requip XL* and by 12 patients (8%) who received IR *Requip*. Adverse events reported as severe in intensity by two or more patients in either treatment group were hallucinations (two patients receiving *Requip XL*), nausea (two patients receiving IR *Requip*) and somnolence (two patients receiving IR *Requip*). Adverse events leading to withdrawal of more than one patient per treatment group were hallucinations (three patients receiving *Requip XL*, one patient receiving IR *Requip*) and hypoaesthesia (two patients, both receiving IR *Requip*).

The type of adverse reactions and the frequency (i.e., incidence) with which they occurred were generally similar over the whole treatment period for patients who were initially treated with *Requip XL* or IR *Requip* and subsequently crossed over to treatment with the other formulation.[49] The proportion of patients with adverse events during the on-treatment phase by dose at onset are summarized in Table 15 and Table 16.

Table 15. Percentage of Patients With the Most Common Adverse Events (AEs ≥ 5%) by Dose at Onset: *Requip XL*

	Daily Dose (mg)							
	2	**4**	**6**	**8**	**12**	**16**	**20**	**24**
Requip XL	**n=77**	**n=85**	**n=80**	**n=101**	**n=78**	**n=66**	**n=50**	**n=34**
All AEs	19%	16%	15%	26%	37%	32%	36%	53%
Nausea	8%	7%	8%	6%	5%	9%	6%	15%
Somnolence	3%	1%	1%	2%	5%	6%	0%	12%
Dizziness	1%	1%	1%	2%	1%	5%	2%	3%
Headache	4%	1%	3%	2%	1%	2%	2%	6%
Constipation	0%	0%	0%	3%	1%	0%	4%	3%
Dyspepsia	1%	0%	0%	0%	0%	3%	2%	0%
Fatigue	0%	1%	0%	<1%	0%	2%	0%	0%

Table 16. - See Appendix

There was an indication of an increase in the overall frequency of adverse events with increasing dose for both formulations. However, when interpreting these data, it should be noted that patients were generally exposed to the lower doses of each formulation for shorter periods of time than for higher doses. This difference in duration of exposure for different doses may have a confounding effect on the frequency of adverse events by dose (i.e., if a patient is observed over a longer period of time the likelihood of the patient experiencing an adverse event would be expected to increase). No particular trends were observed for the frequency of any of the most common adverse events by dose.

5.4 Onset of Dyskinesia in Patients Receiving *Requip XL* for PD (Adjunct Therapy)

Study Description

A multicenter, randomized, double-blind, parallel-group, L-dopa-controlled, flexible-dose study evaluated the time to onset of dyskinesia during adjunctive therapy with *Requip XL* compared to adjunctive L-dopa.[29] Patients included in the study had a diagnosis of idiopathic Parkinson's disease (PD) (Hoehn & Yahr stage I–III), had been taking ≤600 mg L-dopa for up to 3 years without optimal symptom control (e.g. mild wearing off or simple on/off fluctuations), and were receiving stable doses of L-dopa for at

least 4 weeks prior to screening. Patients were randomized (1:1) to add-on *Requip XL* or L-dopa for 104 weeks. Patients were titrated from *Requip XL* 2 mg/day or L-dopa 50 mg/day until an optimal therapeutic dose was achieved (maximum of *Requip XL* 24 mg/day or L-dopa 1000 mg/day). Doses were adjusted weekly if appropriate. No reduction in baseline L-dopa dose was permitted. If they did not experience a reduction in symptoms following up titration through eight dose levels, patients were withdrawn from the study. Please note, the dosing for *Requip XL* in this study differs from the approved prescribing information for *Requip XL*.

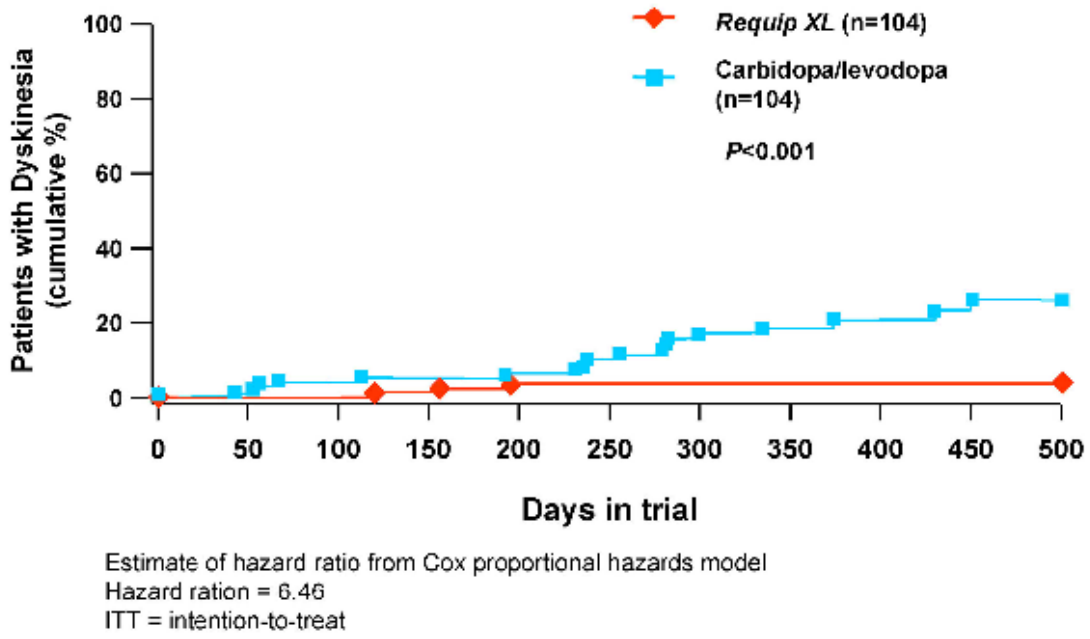
The study was terminated early for reasons unrelated to safety or tolerability. Almost 2 years after initiation, a review of the study indicated that enrollment was lower than the projected sample size needed. A subsequent analysis of blinded preliminary data showed a low rate of dyskinesia, based on the study's original statistical assumptions which rendered continuation of the study futile. Analysis of the final data set, however, revealed a higher rate of dyskinesia. In addition, the difference in dyskinesia rates between the two treatment groups was higher than the projected difference on which the original sample size calculations were based. Due to early termination of the study, the analysis was based on a smaller number of patients than planned.

The primary efficacy endpoint was the time to onset of dyskinesia with adjunctive *Requip XL*, compared to adjunctive L-dopa. Secondary endpoints included the following: mean change from baseline to Week 104 LOCF in the Unified Parkinson's Disease Rating Scale (UPDRS) activities of daily living (ADL; part II) and UPDRS total motor score (part III). For the primary analysis, events (onset of dyskinesia) were censored at the end of the study (Week 104).

Study Results

A total of 208 patients were included in the intent-to-treat (ITT) analysis (*Requip XL*, n=104; L-dopa, n=104).[29] Patient demographics and baseline characteristics were similar between the treatment groups. At baseline, the mean (standard deviation [SD]) dose of L-dopa was 369 (168) mg/day in the group receiving *Requip XL* and 364 (212) mg/day in the L-dopa group. At week 104 (LOCF), the mean (SD) doses of adjunctive *Requip XL* and L-dopa were 10 (6.2) mg/day and 284 (222) mg/day, respectively. In total, 48% of patients receiving *Requip XL* and 43% of patients in the L-dopa group received study medication for ≥ 1 year. The mean (SD) duration of exposure to study medication during the maintenance period was 335 (168) days with *Requip XL* and 308 (164) days with L-dopa. Overall, 21 patients developed dyskinesia (*Requip XL*, n=3 [3%]; L-dopa, n=18 [17%]) during the study. There was a statistically significant delay in the onset of dyskinesia for patients treated with *Requip XL*, compared with patients treated with L-dopa (P <0.001) (Figure 14).

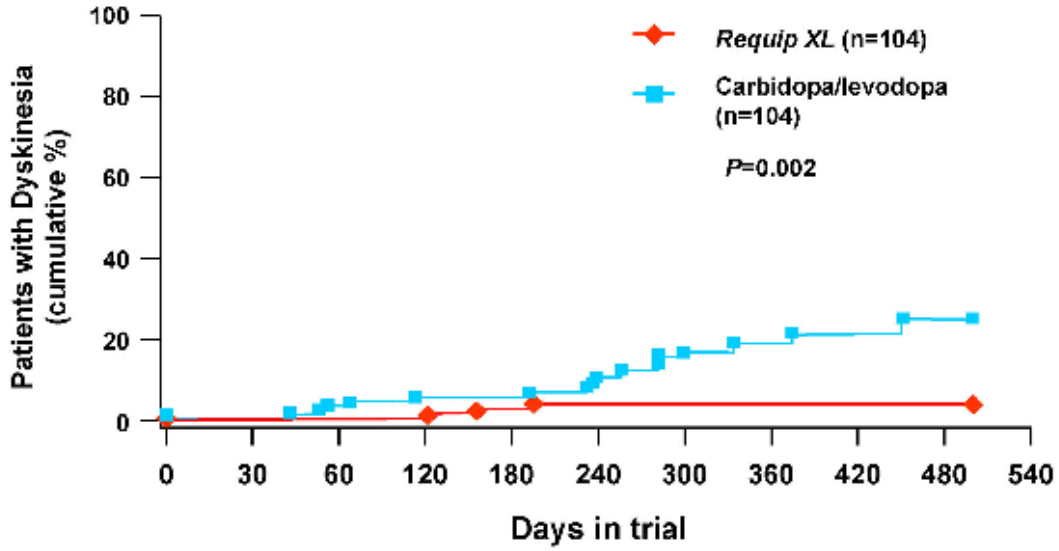
Figure 14. Time to Onset of Dyskinesia (ITT Population)



Estimate of hazard ratio from Cox proportional hazards model
Hazard ration = 6.46
ITT = intention-to-treat

A post-hoc analysis with censoring of observations after the investigators were informed that the trial was being terminated also showed a significant delay in the onset of dyskinesia in the group receiving *Requip XL* versus the L-dopa group ($P = 0.002$) (Figure 15).

Figure 15. Time to Onset of Dyskinesia (ITT Population) [Observations censored at time of decision to terminate study]



Estimate of hazard ratio from Cox proportional hazards model
Hazard ration = 5.75
ITT = intention-to-treat

Another post-hoc analysis with removal of eight patients (four in each treatment group) with evidence of dyskinesia at baseline, showed a significant delay in the onset of dyskinesia in patients receiving *Requip XL* compared to L-dopa ($P = 0.004$). No clinically important between-group differences were seen with *Requip XL*, compared with L-dopa, for change from baseline in UPDRS ADL or UPDRS total motor score.

Safety Results

The most frequently reported adverse events (≥10%) were nausea (*Requip XL* 25% versus L-dopa 15%), dizziness (21% vs. 14%), insomnia (16% vs. 10%), back pain (13% vs. 10%), arthralgia (13% vs. 9%), somnolence (13% vs. 6%), fatigue (10% vs. 9%), and pain in at least one extremity (10% vs. 6%).[29] Adverse events leading to withdrawal were reported in 14% (15/104) of patients receiving *Requip XL* and 9% (9/104) of those receiving L-dopa. Serious adverse events were reported by 16% (17/104) receiving *Requip XL* and 14% (15/104) receiving L-dopa. None of which were considered related to study medication.

6. OUTCOME AND ECONOMIC EVALUATION

6.1 Medication Adherence in Patients with PD (General)

Observational Studies and Clinical Outcomes

Several studies have evaluated medication adherence in patients taking PD medications.[1,2,7,8] Poorer patient medication compliance was found to be associated with younger patient age, patients taking more tablets per day, higher depression scores, poorer quality of life and worsening of PD symptoms.

A 3-month, single-center, observational study evaluated the adherence to PD medication and the effects on clinical outcomes in 54 patients (taking 117 medications).[7] Of the 54 evaluable patients, 11 (20%) were classified as underusers (total compliance of < 80%) and 43 (80%) had satisfactory adherence (total compliance > 80%). Underusers had median total dose compliance of 65% (interquartile range [IQ], 37-74) versus 98% (IQ, 93-102) in the satisfactory adherence group. Median daily compliance was 84% (IQ, 67-90) in satisfactory users versus 27% (IQ, 4-37) for underusers. Median time interval compliance (number of doses taken in the correct time interval) was 11% in underusers (IQ, 2-20) and 25% in those with satisfactory adherence (IQ, 11-73). Poorer compliance (total, daily and timing) was significantly associated with younger age, taking more PD medication tablets per day (daily), higher depression scores (total), and with poorer quality of life (total). Fifty-six percent of once daily medications had time interval compliance of >80% versus 3% of medications prescribed twice daily or more. Changes in UPDRS II, III, Hoehn and Yahr, and Schwab and England and rates of adverse events did not differ between groups.

Adherence was monitored for 1 month in a study of 39 patients with PD, using a medication questionnaire and a computerized medication event monitoring system (MEMS).[1] All patients were taking multiple medications (5.2±0.4) with a mean number of 3.9±0.2 doses per day. The MEMS bottle was used for the following medications: carbidopa-levodopa (n = 10), carbidopa-levodopa extended-release (n = 13), pergolide (n = 7), pramipexole (n = 4), ropinirole (n = 4), and trihexyphenidyl (n = 1). According to the MEMS, only 4 of 39 patients had complete schedule adherence (no missed, extra, or mistimed doses). Using a questionnaire, 24.3% of subjects admitted missing any doses but the computerized MEMS recorded that 19 patients had missed less than one dose, 12 had missed one to three doses and eight missed more than three doses per week. Mistiming of doses was admitted by 73% of patients but 82.1% had recorded mistimed doses. When < 80% of doses taken correctly was used to define nonadherence, 15.3% were considered nonadherent. When < 90% of doses taken correctly was used, 28.1% were considered nonadherent. Of patients reporting a reason for nonadherence, "being too busy" was the most common (85.7%) response. Gender (P=0.03) and level of education (P=0.04) were statistically related to nonadherence.

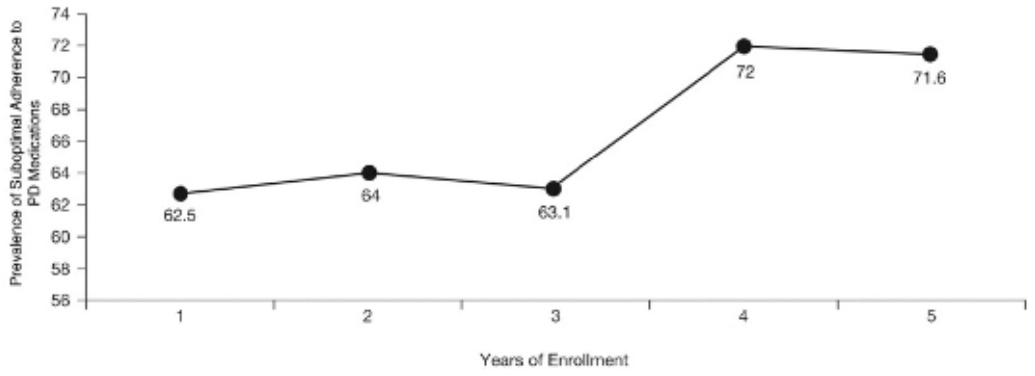
Retrospective, Longitudinal Cohort Study in Medicare Health Maintenance Organization

The prevalence of poor medication adherence (measured by medication possession ratio [MPR= the days of PD prescription dispensed divided by the number of days between refills]) to PD medications, and its effect on worsening of PD symptoms was assessed in a retrospective, longitudinal cohort study of 104 patients with PD (>65 years) in a Medicare health maintenance organization population.[2] Worsening

of PD symptoms was measured as increase in monotherapy dose, augmentation of therapy, PD-related emergency department visit, or hospitalization. Assuming a prescription filled was a prescription taken, refill patterns were used to assess adherence.

An MPR of 80% was considered a reasonable threshold for persistence. A sensitivity analysis was performed with different thresholds of the MPR scores implying suboptimal adherence. The population was grouped in two categories: younger adults (65–75 years of age) and older adults (76 years of age and older). A severity-of-comorbidity index assigned was weighted for a number of major conditions (ranging from 1 to 6). In all 5 years, characteristics of the study sample included: average age of 80 years, even distribution of males and females, average Charleson index of 3.7, average MPR ranging from 0.42 (±0.37) to 0.55 (±0.37). When MPR scores of < 0.8 were used to define suboptimal adherence, approximately 67% of patients were considered to be sub-optimally adherent to their PD medications (Figure 16).

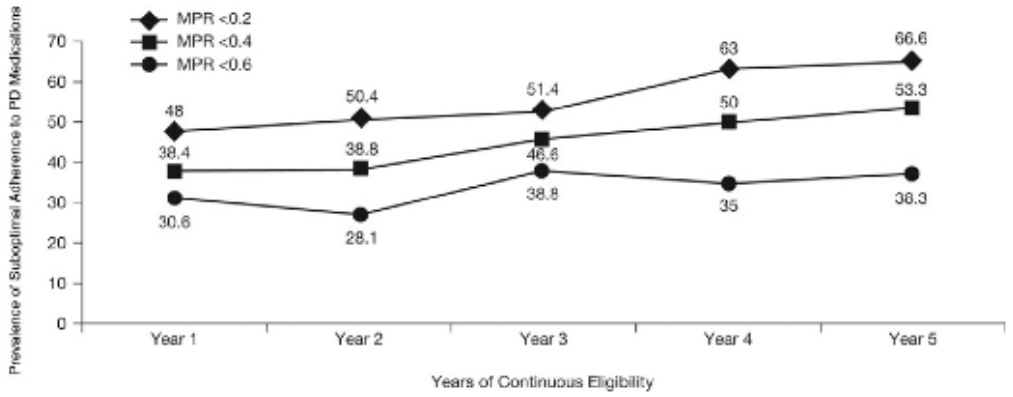
Figure 16. Prevalence of Suboptimal Adherence to Parkinson's Disease Medications*



* medication possession ratio < 0.8

When an MPR threshold of 0.2 was used, approximately 35% were suboptimally adherent (Figure 17).

Figure 17. Prevalence of Suboptimal Adherence to Parkinson's Disease Medication by Medication Possession Ratio (MPR)



* **MPR** = medication possession ratio

There was a strong negative association between adherence and worsening of PD symptoms based on logistic regression analysis. When suboptimal adherence was defined as MPR scores < 0.8, the odds of patients adherent to PD medications experiencing a worsening of PD symptoms was 0.33 (67% less), compared with the odds of patients suboptimally adherent to medications (confidence interval: 0.13–0.85).

See Table 17. When the MPR was reduced to 0.4, the odds of patients adherent to their PD medications experiencing a worsening of PD symptoms was 0.03 (97% less) compared with the odds of patients who were suboptimally adherent to their PD medications (confidence interval: 0.004–0.28).

Table 17. Worsening of Parkinson's Disease Symptoms Association with Adherence to Parkinson's Disease Medications Across 5 Years(2)

	Worsening of Parkinson's disease symptoms		
	MPR < 0.8	**MPR < 0.6**	**MPR < 0.4**
	Odds ratio* (95% confidence Interval)		
Adherence	0.33 (0.13–0.85)†	0.12 (0.03–0.39)†	0.03 (0.004–0.28)†
Number of outpatient visits	1.30 (1.00–1.70)†	1.37 (1.04–1.80)‡	1.42 (1.08–1.86)‡
Patients aged >75 years	0.96 (0.34–2.72)	1.04 (0.36–3.02)	1.15 (0.39–3.37)
Male sex	0.49 (0.19–1.28)	0.48 (0.18–1.27)	0.42 (0.15–1.12)
Year 1 dummy	1.03 (0.21–5.09)	1.31 (0.25–6.68)	1.28 (0.24–6.61)
Year 2 dummy	0.77 (0.17–3.40)	0.95 (0.21–4.32)	1.04 (0.22–4.81)
Year 3 dummy	2.88 (0.45–18.39)	3.53 (0.53–23.27)	3.33 (0.49–22.35)
Year 4 dummy	0.78 (0.18–3.38)	0.80 (0.18–3.59)	0.77 (0.16–3.53)

* Reference groups were female sex, patients aged ≤75 years, and Year 5

† P=.01

‡ P=0.05

MPR = medication possession ratio

Self-Reported Adherence vs. Pill Count

Adherence data from two NET-PD Phase II clinical trials (n = 413) were analyzed to compare the Morisky medication adherence questionnaire to pill counts as measures of adherence and to evaluate the association between demographic and clinical characteristics and adherence.(8) Patients took study drug twice daily in one trial and four times daily in the other. The average percent of study drug taken (assessed by pill count) ranged from 92-94% across both studies. Ninety-percent of patients took 80% or more of the study drug. The Morisky medication adherence questionnaire showed 56% report high and 44% report medium adherence. Agreement between the two measures is fair (ICC = 0.40). Older age, higher baseline UPDRS motor scores, and lower Geriatric Depression scores were associated with better adherence. Gender, disease duration, education level, quality of life or activities of daily living were not predictors of adherence in this study.

6.2 Medication Adherence in Patients with PD (IR *Requip*)

Survey of PD Patients Taking IR Requip

A survey of 250 patients with Parkinson's disease (PD) who were taking IR *Requip* at least three times daily (TID) was conducted to determine medication adherence, patient-reported drivers and consequences of nonadherence and interest in a once-daily formulation of *Requip*.(9) Patients were primarily white (90%) males (62%) with a mean age of 67 years and a Hoehn & Yahr Stage 2 (49%). Most patients (80%) were receiving *Requip* TID at a mean daily dose of 7 mg with 55% of patients receiving concomitant L-dopa. Thirty-six percent of patients were receiving monotherapy with IR *Requip*.

Sixty-seven percent of patients were categorized as non-adherent to their medication, with only 33% categorized as adherent (no missed doses of IR *Requip* in the past week). Nonadherence was commonly attributed to forgetting to take IR *Requip* as prescribed (44%), forgetting to take their medication with them (35%) and being too busy (31%). Nonadherence resulted in the following PD symptoms: increase in tremors (43%), bradykinesia (34%), difficulty concentrating (25%), freezing (24%) and difficulty moving (24%). These PD symptoms occurred as early as 1 hour after missing a dose and interfered with work (44%) and social (49%) activities, sleep (33%), mood (28%), concentration (36%) and overall quality of life (61%). Eighty-eight percent of patients indicated interest in a once-daily formulation of *Requip* because it would be easy to remember to take.

6.3 Daily Pill Burden in Patients with PD

Complex medication regimens, including taking multiple medications or frequent dosing, have been linked to poor medication adherence in patients with PD as well as in other chronic conditions.[1,2,3,4,5,6] An analysis was conducted to document the daily pill burden of patients with Parkinson's disease enrolled in U.S. managed care plans and to evaluate the potential need for *Requip XL*, a once-daily regimen.[10]

This retrospective, cross-sectional database analysis study used pharmacy and medical claims from the Integrated Healthcare Information Services (IHCIS) National Managed Care Benchmark Database.[10] The data contained over 60 million lives from at least 45 health plans at the time of analysis. The IHCIS database system is a comprehensive, de-identified U.S. healthcare claims database that is representative of the non-elderly, insurance-carrying population in the US. All prescription fills for antiparkinsonian medications were identified for each patient during April 1 to 14, 2006. Using a 2-week identification period should limit the number of people getting refills (i.e., April 1st and 28th) and switching thereby creating a conservative estimate for daily pill burden. Patients were divided into 3 categories: IR *Requip*, Mirapex® (pramipexole), and Other (i.e., patients filling an antiparkinsonian medication other than IR *Requip* or pramipexole). Any use of *Requip XL* will likely come from patients previously taking IR *Requip* and pramipexole due to their similar mechanisms of action. The daily pill burden of patients in the "Other" Group is included to complete the picture of daily pill burden experienced by patients with Parkinson's disease. All patients were required to have had a primary diagnosis of Parkinson's disease (ICD-9 code 332.XX) anytime from January 1998 to December 2006.

Daily pill burden was calculated for the total cohort as well as the groups for IR *Requip*, pramipexole, and other. Two patients filling prescriptions for both IR *Requip* and pramipexole were excluded since there is no clinical rationale to take these drugs simultaneously. A third patient filling pramipexole was excluded due to a data entry error for the number of pills dispensed (~2,400 in the 2-week period). There were 2,299 total unique patients identified. The mean daily pill burden for all patients was 5.1 (SD 4.2) antiparkinsonian medication tablets, with 75% of patients taking at least 3 pills per day. Patients in the group receiving IR *Requip* (n=342; 15%) took an average of 4.1 (SD 2.9) tablets of IR *Requip* per day and 6.2 (SD 5.2) tablets when considering all antiparkinsonian medications in addition to IR *Requip*. Approximately 44% (n=151/342) of patients in the group receiving *Requip* filled at least one adjuvant antiparkinsonian prescription during the 2-week identification period. Patients in the pramipexole group (n=475; 21%) took an average of 3.8 (SD 2.0) pramipexole tablets per day and 5.8 (SD 3.9) tablets when considering all antiparkinsonian medications in addition to pramipexole. Approximately 44% (n=208/475) of patients in the pramipexole group filled at least one adjuvant antiparkinsonian prescription during the 2-week identification period. Patients in the other group (n=1482; 64%) took an average of 4.6 (SD 4.0) antiparkinsonian medication tablets daily.

This analysis indicates that many patients with Parkinson's disease face significant daily pill burden and complex dosing regimens to manage their disease. It highlights the need for treatment options that can reduce this burden.

6.4 Effect of *Requip XL* on Quality of Life in PD

Please see Section 4.2 of the Dossier - Quality of Life Endpoint Results.

REFERENCE(S)

1. Leopold NA, Polansky M, Hurka MR. Drug adherence in Parkinson's disease. Mov Disord 2004;19(5):513-317.*
2. Kulkarni AS, Balkrishnan R, Anderson RT. Medication adherence and associated outcomes in medicare health maintenance organization-enrolled older adults with Parkinson's disease. Mov Disord 2008;23(3):359-365.*
3. Nausieda PA, Pfeiffer RF, Tagliati M, et al. Multicenter, open-label, sequential study comparing preferences for carbidopa-levodopa orally disintegrating tablets and conventional tables in subjects with Parkinson's disease. Clin Ther 2005;27:58-63.*

4. Grosset KA, Reid JL, Grosset DG. Medication-taking behavior: implications of suboptimal compliance in Parkinson's disease. Mov Disord 2005;20:1397-1404.*
5. Cramer JA. Systematic review of adherence with medications for diabetes. Diabetes Care 2004;27:1218-1224.*
6. Claxton AJ, Cramer J, Pierce C. A systematic review of the association between dose regimens and medication compliance. Clin Ther 2001;23:1296-1310.*
7. Grosset KA, Bone I, Grosset DG. Suboptimal medication adherence in Parkinson's disease. Mov Disord 2005;20(11):1502-1507.*
8. Elm JJ, Kamp C,Tilley BC, et al. Self-reported adherence versus pill count in Parkinson's disease: the NET-PD experience. Move Disord 2007;22(6):822-7.*
9. Edin HM, DiBenedetti DB and Hill CD. Adherence among Parkinson's disease patients taking ropinirole immediate release at least thrice daily. Mov Disord 2008;23(Suppl 1):S344(P1058).*
10. RC2007/00088/00. Data on File. *
11. Olanow CW, Watts RL and Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. Neurology 2001;56(Suppl 5):S1-S88.*
12. Miyasaki JM, Martin W, Suchowersky O, et al. Practice parameter: Initiation of treatment for Parkinson's disease: An evidence-based review. Report of the quality standards subcommittee of the American Academy of Neurology. Neurology 2002;58:11-17.*
13. Nutt JG. On-off phenomenon: relation to levodopa pharmacokinetics and pharmacodynamics. Ann Neurol 1987;22:535-540.*
14. Olanow CW, Agid Y, Mizuno Y, et al. Levodopa in the treatment of Parkinson's disease: current controversies. Mov Disord 2004;19:997-1005.*
15. Chase T, Engber T and Mouradian MM. Palliative and prophylactic benefits of continuously administered dopaminomimetics in Parkinson's disease. Neurol 1994;44(7Suppl 6):S15-S18.*
16. Chase TN. The significance of continuous dopaminergic stimulation in the treatment of Parkinson's disease. Drugs 1998;55(Suppl. 1):1-9.*
17. Olanow CW, Obeso JA and Stocchi F. Continuous dopamine-receptor treatment of Parkinson's disease. Lancet Neurol 2006;5:677-687.*
18. Stockwell KA, Virley DJ, Perren M, et al. Continuous delivery of ropinirole reverses motor deficits without dyskinesia induction in MPTP-treated common marmosets. Exp Neurol 2008;211:172-179.*
19. Requip®XL™. Prescribing Information.*
20. Tompson DJ and Vearer D. Steady-state pharmacokinetic properties of a 24-hour prolonged-release formulation of ropinirole: results of two randomized studies in patients with Parkinson's disease. Clin Ther 2007;29(12):2654-2666. Study 164, Study 165.*
21. Schapira AHV, Stocchi F, Hunter B and Giorgi L. Comparison of adjunctive ropinirole prolonged release and ropinirole immediate release in patients with advanced Parkinson's disease: a post-hoc per-protocol analysis of the PREPARED study. Mov Disord 2008;23(Suppl 1):S196(P594).*
22. Stocchi F, Hunter B, Giorgi L and Schapira AVH. Comparison of adjunctive ropinirole prolonged release and ropinirole immediate release in patients with advanced Parkinson's disease: the PREPARED study. Mov Disord 2008;23(Suppl 1):S215(P655).*
23. Schapira AHV, Stocchi F, Hunter B, et al. Adjunctive ropinirole prolonged release compared with adjunctive ropinirole immediate release in patients with advance Parkinson's disease: results from a *post-hoc* per-protocol analysis of the PREPARED study. Eur J Neurol 2008;15(Suppl 3):131 (#P1365).*
24. Stocchi F, Hunter B, Giorgi L, et al. Adjunctive ropinirole prolonged release compared with adjunctive ropinirole immediate release in patients with advance Parkinson's disease: the PREPARED study. Eur J Neurol 2008;15(Suppl 3):134 (#P1373).*
25. Stocchi F, Hunter B, Giorgi L, et al. An evaluation of symptom control in patients with advanced Parkinson's disease receiving adjunctive ropinirole prolonged release versus ropinirole immediate release: results from the PREPARED study. Eur J Neurol 2008;15(Suppl 3):134 (#P1374).*
26. Data on File. ROP105323. 2008. *
27. Pahwa R, Stacy MA, Factor SA, et al. Ropinirole 24-hour prolonged release: randomized, controlled study in advanced Parkinson disease. Neurology 2007;68:1108-1115. Study 169.*

28. Stocchi F, Hersh BP, Scott BL, et al. Ropinirole 24-hour prolonged release and ropinirole immediate release in early Parkinson's disease: a randomized, double-blind, non-inferiority crossover study. Curr Med Res Opin 2008;24(10):2883-2895. Study 168.*
29. Data on File. SKF-101468/228. 2007. *
30. Boothman BR, Grosset DG. Ease of overnight switching from immediate release ropinirole to once-daily prolonged release ropinirole in early parkinson's disease. European Journal of Neurology 2006;13(Suppl 2):88(P1174).*
31. Pahwa R and Lyons KE. An open-label conversion study of pramipexole to ropinirole prolonged release in patients with Parkinson's disease. Mov Disord 2008;23(Suppl 1):S314 (P961).*
32. Gelb DJ, Oliver E, Liman S. Diagnostic criteria for Parkinson's disease. Arch Neurol 1999;56:33-9.*
33. Olanow CW and Koller WC. An algorithm (decision tree) for the management of Parkinson's disease: treatment guidelines. Neurology 1998;50(Suppl 3):S1-S57.*
34. US interim projections by age, sex, race and Hispanic origin. US Census Bureau, 2004. Available at: http://www.census.gov/ipc/www/usinterimproj/. Accessed August 11, 2005 *
35. Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976-1999. Neurology 1999;52:1214-1220.*
36. Marras C and Tanner CM. In: Watts RL and Koller WC. Movement Disorders: Neurologic Principles & Practice. 2nd ed 2004;1976-1999.*
37. Wooten GF, Curre LJ, Bovbjerg VE, et al. Are men at greater risk for Parkinson's disease than women. J Neurol Neurosurg Psychiatry 2004;75:637-639.*
38. Murdoch D, Cheer SM, Wagstaff AJ. Management of Parkinson disease: defining the role of ropinirole. Dis Manage Health Outcomes 2004;12(1):39-54.*
39. Suchowersky O, Reich S, Perlmutter J, et al. Practice parameter: diagnosis and prognosis of new onset Parkinson disease (an evidence-based review): report of the Quality Standards Ssubcommittee of the American Academy of Neurology. Neurology 2006;66:968-975.*
40. Schapira A. Treatment options in the modern management of Parkinson disease. Arch Neurol 2007;64(8):1083-1088.*
41. Conte U and Maggi L. Modulation of the dissolution profiles from Geomatrix® multi-layer matrix tablets containing drugs of different solubility. Biomaterials 1996;17(9):889-896.*
42. Conte U, Maggi L, Colombo P, La Manna A. Multi-layered hydrophilic matrices as constant release devices (Geomatrix™ Systems). J Contr Rel 1993;26:39-47.*
43. Colombo P, Catellani PL, Peppas NA, et al. Swelling characteristics of hydrophilic matrices for controlled release: new dimensionless number to describe the swelling and release behavior. Int J Pharm 1992;88:99-109.*
44. Colombo P, Conte U, Gazzaniga A, et al. Drug release modulation by physical restrictions of matrix swelling. Int J Pharm 1990;63:43-48.*
45. Conte U, Maggi L, Torre ML, et al. Press-coated tablets for time-programmed release of drugs. Biomaterials 1993;14(13):1017-1023.*
46. Rao KVR, Devi KP, Buri P. Influence of molecular size and water solubility of the solute on its release from swelling and erosion controlled polymeric matrices. J Contr Rel 1990;12:133-141.*
47. Eden RJ, Costall B, Domeney AM, et al. Preclinical pharmacology of ropinirole (SK&F 101468-A) a novel dopamine D_2 agonist. Pharmacol Biochem Behavior 1991;38:147-154.*
48. Data on File. SKF-101468/164. 2007. *
49. Data on File. SKF-101468/168. 2005. *
50. Stocchi F and Giorgi L. Efficacy or ropinirole 24-hour prolonged release compared with immediate release formulation in early Parkinson's disease (PD): the EASE-PD monotherapy study. Eur J Neurol 2006;13(Suppl 2):205(P2141) (168).*
51. Stocchi F, Hersh BP, Earl NL, et al. Safety and tolerability of ropinirole 24-hour prolonged release in patients with early and advanced Parkinson's disease. Mov Disord 2006;21(Suppl 15):S572(P894) (168).*
52. Stocchi F, Hersh B and Giorgi L. Safety and tolerability of ropinirole 24-hour prolonged release in patients with early and advanced Parkinson's disease (PD). Eur J Neurol 2007;14(Suppl 1):76(P1175) (168).*

53. Hauser RA, Factor SA, Hersh BP. Ropinirole 24-hour prolonged release improves mood and reduces "off" time as adjunctive therapy in patients with parkinson's disease. 59th American Academy of Neurology Annual Meeting, Boston, MA, April 28 – May 5, 2007 *
54. Stover N, Isaacson S, Elmer L. Adjunctive ropinirole 24-hour prolonged release improves patient-reported outcomes of depression, quality of life, and sleep in advanced Parkinson's disease. 132nd Annual Meeting of the American Neurological Association, Washington D.C., 7–10 October, 2007 *
55. Giorgi L and Hunter B. Adjunctive ropinirole prolonged release improves the patient-reported outcomes of sleep and quality of life in advanced Parkinson's disease. Eur J Neurol 2008;15(Suppl 3):113 (#P1302).*
56. Data on File. Study SKF-101468/169. 2008. *

Appendix

Table 11. Dose Switches Between Formulations

IR *Requip to Requip XL*		*Requip XL to* IR *Requip*	
Total Daily Dose of IR *Requip* (mg)	**Total Daily Dose of *Requip XL* (mg)**	**Total Daily Dose of *Requip XL* (mg)**	**Total Daily Dose of IR *Requip* (mg)**
0.75 - 2.25	2	2	2.25
3 - 4.5	4	4	4.5
6	6	6	6
7.5 - 9	8	8	7.5
12	12	12	12
15 - 18	16	16	15
21	20	20	21
24	24	24	24

Table 12. Results for Dose and UPDRS Motor Scores†

	End of Titration Phase (week 12)	**End of first flexible-dose maintenance period (week 20)**	**End of second flexible-dose maintenance period (week 28)**	**End of third flexible-dose maintenance period (week 36)**
Mean (SD) dose:				
Requip XL	18.0 (5.7)	18.6 (5.7)	14.0 (7)	9.6 (5.7)
IR *Requip*	7.0 (2.1)	8.9 (4.6)	13.9 (7.7)	18.8 (5.9)
Mean (SD) change from period baseline* in UPDRS motor score:				
Requip XL	–10.4 (6.1)	0.0 (4)	–0.2 (3.8)	–0.4 (3)
IR *Requip*	–8.9 (5.9)	0.5 (3.1)	0.6 (2.7)	0.7 (2.5)

Key: SD= Standard Deviation; UPDRS=Unified Parkinson's Disease Rating Scale

* Period baseline was the end of the previous phase/period (or overall baseline for the titration phase).

† Scores are observed cases for week 12 and last observation carried forward for other time points

Note: Higher mean doses of *Requip XL* vs. IR *Requip* at the end of the titration phase were due to its titration regimen which allowed a faster titration. These higher doses were not due to lower potency of *Requip XL*.

Table 13. Results for Secondary Endpoints†

	End of Titration Phase (week 12)	End of first flexible-dose maintenance period (week 20)	End of second flexible-dose maintenance period (week 28)	End of third flexible-dose maintenance period (week 36)
Patients (%) scoring 1 or 2 on CGI-I scale:				
Requip XL	37/53 (70%)	37/53 (70%)	38/62 (61%)	27/47 (57%)
IR *Requip*	24/54 (44%)	30/53 (57%)	25/38 (66%)	28/47 (60%)
Patients (%) with a 30% reduction in UPDRS motor score:				
Requip XL	54/70 (77%)	49/66 (74%)	48/69 (70%)	37/58 (64%)
IR *Requip*	53/80 (66%)	51/67 (76%)	36/55 (65%)	35/48 (73%)
Mean (SD) change from period baseline* in UPDRS ADL score:				
Requip XL	–3.2 (2.9)	–0.1 (1.4)	0.2 (2.6)	0.1 (2.1)
IR *Requip*	–3.1 (2.8)	0.1 (1.6)	–0.1 (1.1)	0.3 (1.9)
Mean (SD) change from period baseline* in BDI score:				
Requip XL	–0.7 (5.7)	0.5 (3.8)	–0.6 (5.2)	0.0 (3.4)
IR *Requip*	–1.4 (4.8)	0.1 (4.4)	–1.5 (5.2)	0.8 (4.6)
Mean (SD) change from period baseline* in ESS score:				
Requip XL	0.7 (2.9)	0.5 (2.7)	0.3 (3)	–0.3 (2.7)
IR *Requip*	0.2 (2.8)	0.1 (2.5)	0.1 (2)	–0.4 (3)
Mean (SD) change from period baseline* in PDSS score:				
Requip XL	3.5 (24.5)	1.2 (16.6)	0.3 (15.3)	–1.0 (11.4)
IR *Requip*	5.8 (15.9)	2.6 (12.7)	–1.1 (15.4))	–3.3 (15)

Key:ADL=Activities of Daily Living; BDI = Beck Depression Inventory; CGI-I=Clinical Global Impresssion-Improvement; ESS= Epworth Sleepiness Scale; PDSS=Parkinson's Disease Sleep Scale; SD= Standard Deviation; UPDRS=Unified Parkinson's Disease Rating Scale

* Period baseline was the end of the previous phase/period (or overall baseline for the titration phase).

† Scores are observed cases for week 12 and last observation carried forward for other time points

Table 16. Percentage of Patients With the Most Common Adverse Events (AEs ≥ 5%) by Dose at Onset: IR *Requip*

	Daily Dose (mg)												
	0.75	**1.5**	**2.25**	**3**	**4.5**	**6**	**7.5**	**9**	**12**	**15**	**18**	**21**	**24**
IR *Requip*	**n=86**	**n=84**	**n=82**	**n=81**	**n=77**	**n=68**	**n=62**	**n=43**	**n=36**	**n=19**	**n=6**	**n=20**	**n=27**
All AEs	13%	19%	21%	25%	30%	35%	27%	40%	33%	42%	50%	20%	41%
Nausea	3%	7%	5%	9%	5%	1%	8%	9%	6%	5%	0%	5%	19%
Somno-lence	1%	0%	1%	1%	4%	10%	5%	5%	8%	16%	33%	5%	4%
Dizziness	0%	0%	2%	2%	1%	3%	3%	2%	6%	0%	0%	0%	0%
Headache	2%	1%	1%	2%	0%	0%	0%	2%	0%	5%	0%	5%	4%
Constipa-tion	1%	2%	0%	1%	3%	0%	0%	2%	0%	0%	0%	5%	4%
Dyspepsia	0%	1%	1%	0%	0%	6%	2%	0%	3%	5%	0%	5%	0%
Fatigue	0%	2%	1%	1%	0%	1%	2%	0%	3%	0%	0%	0%	4%